Paper No. 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENERAL ELECTRIC CO.
Petitioner,

v.

UNIVERSITY OF VIRGINIA PATENT FOUNDATION,
Patent Owner

Patent No. RE45,725
Issued: October 6, 2015
Filed: October 14, 2013
Inventors: John Mugler III, *et al.*
Titled: Method and apparatus for spin-echo-train MR imaging using prescribed signal evolutions

Inter Partes Review No. IPR_________

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. RE45,725

UNDER 35 U.S.C. § 312 AND 37 C.F.R. § 42.104

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Exhibit No.	*Description*
	single-slab, 3-dimensional, T2-weighted turbo-spin-echo sequence with high sampling efficiency (SPACE) for high spatial resolution imaging: initial clinical experiences," Investigative Radiology, Vol. 40, pp. 754-60 (2005) ("Kiefer 2005")
1024	Patent Owner's November 13, 2015 Letter submitted in the GE Litigation to the Court
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I. INTRODUCTION AND STATEMENT OF RELIEF REQUESTED (37 C.F.R. § 42.22(A))

General Electric Co. D/B/A GE Healthcare ("Petitioner") petitions for the institution of *inter partes* review of claims 47-80 (the "Challenged Claims") of U.S. Patent No. RE45,725 to John P. Mugler, III,, *et al* ("the '725 Patent," attached as Ex. 1001). USPTO records indicate that the '725 Patent is assigned to University of Virginia Patent Foundation ("P.O."), which is currently asserting the '725 Patent against Petitioner in a concurrent litigation. *See* Ex. 1012.

II. MANDATORY NOTICES

A. Real Party-in-Interest

General Electric Co. (Petitioner) is the real party-in-interest.

B. Related Matters

P.O. has sued Petitioner in the U.S. District Court for the Western District of Virginia, alleging infringement of the '725 Patent (Ex. 1001). *UVAPF v. General Electric Co.*, No. 3:14-cv-00051-nkm ("GE Litigation"). On October 16, 2015, P.O. filed a motion for leave "request[ing] that the Court permit UVAPF to file [an] amended complaint" adding the '725 Patent. Ex. 1008. On October 19, 2015, the Court granted P.O.'s motion for leave (Ex. 1011), and P.O. filed an amended complaint asserting the '725 Patent against Petitioner. Ex. 1012.Thus, Petitioner was not "served with a complaint" under § 315(b) until October 19, 2015. *See* *TRW Automotive US v. Magna Elecs., Inc.*, IPR2014-00293, Paper No. 18 at 5-11

(P.T.A.B. June 27, 2014) (holding that, "regardless of any prior 'consent' by a Petitioner," a proposed amended complaint attached to a Patent Owner's motion requesting leave to amend a pleading is "not an actual 'complaint' within the meaning of § 315(b).").

The '725 Patent is a continuation of U.S. Patent No. RE44,644 ("the '644 Patent," Ex. 1007). In the GE Litigation, P.O. also has asserted the '644 Patent. The '644 Patent is the subject of three instituted *inter partes* reviews, styled as *General Electric Co. v. University of Virginia Patent Foundation* in Case Nos. IPR2016-00357, IPR2016-00358, and IPR2016-00359 ("'644 IPRs"). The GE Litigation is stayed until the resolution of the '644 IPRs.

Designation of Lead Counsel (37 C.F.R. § 42.8(b)(3))	**Back-Up Counsel**
Marc S. Kaufman (Reg. #35,212) mskaufman@reedsmith.com REED SMITH, LLP 1301 K Street, NW East Tower – Suite 1000 Washington, DC 20005 Tel: 202.414.9249 Fax: 202.414.9299	David Pollock (Reg. #48,977) dpollock@reedsmith.com Jonathan I. Detrixhe (Reg. #68,556) REED SMITH, LLP 101 Second Street Suite 1800 San Francisco, CA 94105 Tel: 415-543-8700 Fax: 415 391 8269

C. Service Information

Please direct all correspondence to lead and back-up counsel at the above addresses.

III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

IV. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

The Challenged Claims are unpatentable as being anticipated under 35 U.S.C. §§ 102(a),(b) and/or for being obvious under 35 U.S.C. § 103. Specifically:

A. **GROUND 1**: Claims 47-80 are anticipated under §§ 102(a) and/or 102(b) by Mugler et al, "Three-Dimensional T2-Weighted Imaging of the Brain Using Very Long Spin-Echo Trains," Proceedings of the International Society for Magnetic Resonance in Medicine, Eighth Meeting, April 2000 at 687 ("Mugler 2000") (Ex. 1002)

B. **GROUND 2:** Claims 47-80 are obvious under § 103(a) over Mugler 2000 in view of Mugler, "Overview of MR Imaging Pulse Sequences," Physics of MR Imaging, Vol. 7, No. 4, pp. 661-697 (Nov. 1999) ("Mugler Overview") (Ex. 1005)

C. **GROUND 3**: Claims 47-80 are obvious under § 103(a) over Alsop, "The Sensitivity of Low Flip Angle RARE Imaging," Magnetic Resonance in Medicine, Vol. 37, pp. 176-184 ("Alsop") (Ex. 1004) in view of Mugler et al, "Three-Dimensional Spin-Echo-Train Proton-Density-Weighted Imaging Using Shaped Signal Evolutions," Proceedings of the International Society for Magnetic Resonance in Medicine, Seventh Meeting, May 1999 at 1631("Mugler 1999") (Ex. 1003)

D. **GROUND 4**: Claims 47-80 are obvious under § 103(a) based on Alsop in view of Mugler 1999, further in view of Mugler Overview

This Petition is supported by the declaration of Dr. Norbert Pelc (Ex. 1009).

V. OVERVIEW

A. Technical Background

Magnetic resonance imaging (MRI) uses magnetic field and radio frequency (RF) pulses applied to an object, such as anatomical structures in a patient's body, to produce a signal that can be processed into images of the object. An MRI scan uses an ordered combination of RF and gradient pulses, called a pulse sequence, designed to acquire data to from the image. Ex. 1009 ¶¶ 40-42. There are three inherent properties of all matter that are used to distinguish between types of tissues in an MR scan: proton density, T1 relaxation, and T2 relaxation. Because the values of these three properties are different for various substances within the body, the difference in values for particular substances may be exploited to generate contrast to form an image. *Id.* at ¶¶ 45-46. "Spin-echo" and "fast-spin-echo" pulse sequences are well known sequences that have an excitation RF pulse followed by one or more refocusing RF pulses. The pulses are applied at a "flip angle" relative to the main magnetic field.

B. The '725 Patent

(i) Summary of Alleged Invention of the '725 Patent

The Challenged Claims of the '725 Patent are substantially similar to those of the '644 Patent at issue in the '644 IPRs. *See* Ex. 1015. Like the '644 Patent, the '725 Patent generally relates to spin-echo imaging. *See* Ex. 1001 at 3:65-4:6. The

’725 Patent explains its purported advancement over the prior art as incorporating the effect of tissue relaxation in its determination of flip angle values. *See, e.g.*, Ex. 1001 at 3:38-62 (contrasting the prior art, which “derived variable flip-angle series . . . when T1 and T2 relaxation are neglected,” with “[t]he present invention method and apparatus” which “explicitly consider the T1 and T2 relaxation times for the tissues of interest and thereby permit the desired image contrast … .”). Consideration of T1 and T2 relaxation times occurs as part of a 4-step algorithm for calculating the flip angles. Ex. 1001 at 10:33-11:14. It is this algorithm for calculating, or selecting, the flip angles for an MR pulse sequence, which includes the effects of T1 and T2 relaxation, that the ’725 Patent regards as its advancement over the prior art. Ex. 1009 ¶ 51-56.

(ii) The Prosecution History

The ’725 Patent is a continuation of the ’644 Patent, which is a reissue of U.S. Pat. No. 7,164,268 (“the ’268 Patent”) (Ex. 1013). *See* Ex. 1001 at 1. Each claim of the ’268 Patent required a “calculating flip angles” step that includes “i) selecting values of T1 and T2 relaxation times and selecting proton density,” “ii) selecting a prescribed time course of the amplitudes and phases of the radio-frequency magnetic resonance signals . . . .”, and “iii) selecting characteristics of said contrast-preparation step, said data-acquisition step and a magnetization-recovery step . . . .” Ex. 1013 at cls. 1-46.

In contrast, each of the Challenged Claims of the ’725 Patent omits each of the three “selecting” steps in each claim of the ’268 Patent directed to the disclosed algorithm for determining flip angles. Ex. 1001 at cls. 47-80.

(iii) Effective Filing Date Of The Challenged Claims

The ’725 Patent claims the benefit of priority to U.S. Provisional App. No. 60/257,182 (“the ’182 Application”) (Ex. 1014). The priority claim to the ’182 Application is ineffective because the subject matter of the Challenged Claims was not disclosed in the ’182 Application in the manner required by 35 U.S.C. § 112, ¶ 1. *See, e.g.*, *SAP America, Inc. v. Pi-Net Int’l*, Inc., IPR No. 2014-00414, Paper No. 11 at 11-14 (P.T.A.B. August 18, 2014) (relying on § 112 case law is proper in an *inter partes* review to establish effective filing date). It is P.O.’s burden to show that the ’182 Application provides written description support for the Challenged Claims. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed.Cir. 2015)(affirming P.T.A.B. that party asserting that a patent is entitled to the benefit of a provisional filing date has the burden of demonstrating written description support in the provisional application). To comply with the written description requirement, the specification “must describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed.” *Lizardtech*, *Inc. v. Earth Resource Mapping, Inc.,* 424

F.3d 1336, 1345 (Fed Cir. 2005). In particular, the written description must provide sufficient information to indicate to a person of ordinary skill that the inventor had possession of the "**full scope**" of the claims. *See, e.g., In re Wertheim*, 541 F.2d 257, 262-64 (C.C.P.A. 1976) (emphasis added). "[A]ll the limitations must appear in the specification" of the priority application, as "[t]he question is **not whether a claimed invention is an obvious variant** of that which is disclosed in the specification." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis added) (expert testimony that claimed subject matter was "well known" to persons skilled in the art was insufficient to provide written description support and meant, at best, that the claimed subject matter would have been obvious to persons skilled in the art). Rather, "one skilled in the art, reading the original disclosure, **must immediately discern the limitation at issue** in the claims." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Although the exact terms of the claims need not be used *in haec verba* to provide written description*, see Eiselstein v. Frank*, 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed.Cir.1995), "possession" of an invention can only be shown by describing the invention with all its claim limitations, even if they are obvious, and is measured as of the filing date sought. *See, e.g.*, *Lockwood*, 107 F.3d at 1572. The Challenged Claims are directed to an "invention" that was not disclosed as being within the inventor's possession at the time of filing of the '182

Application. Accordingly, the Challenged Claims are not entitled to the effective filing date of the ’182 Application.

(A) The Challenged Claims are directed to the results of an algorithm for determining flip angles while omitting the entirety of the algorithm disclosed by the ’182 Application for achieving those results

The ’182 Application discloses that “**[o]ur method explicitly considers the Tl and T2 relaxation times for the tissues of interest** and **thereby permits** the desired image contrast to be incorporated into the tissue signal evolutions corresponding to the long echo train.” Ex. 1014 at 3 (emphasis added). Likewise, the ’725 Patent states that “**[t]he present invention** method and apparatus **explicitly consider the T1 and T2 relaxation times** for the tissues of interest.” Ex. 1001 at 3:55-57 (emphasis added). Similarly, the ’182 Application states that “**[t]his invention consists** of . . . **for selected T1 and T2 relaxation times**.” *Id.* at 4 (emphasis added). Consistent with the requirement of considering relaxation, the ’182 Application provides a four-step algorithm for determining flip angles that includes, among other steps, selecting “the T1 and T2 relaxation parameters for the ‘target’ tissue.” Ex. 1014 at 6-7. This four-step algorithm is the **only** guidance the ’182 Application provides on how to select flip angles; no other algorithm is disclosed. Ex. 1009 ¶¶ 67-68. As all MR pulse sequences necessarily have flip angle parameters, and the ’182 Application only provides one algorithm for selecting the flip angle parameters, a person of ordinary skill would understand the

’182 Application to require that flip angles be selected using the four-step algorithm in order to achieve the described beneficial results. *Id.* at ¶ 68. Furthermore, in the ’644 IPRs, UVAPF has relied extensively on the four-step algorithm as providing support for the claimed range results. *Id.*

Each Challenged Claim omits the limitation “selecting values of T1 and T2 relaxation times.” Furthermore, there is no requirement in any Challenged Claim that Tl and T2 relaxation times for the tissues of interest be considered in any way, much less explicitly considered. Ex. 1009 ¶ 69. Not only does each Challenged Claim omit consideration of T1 and T2 relaxation times—which is described as “the invention” —but each Challenged Claim also omits the entirety of the four-step algorithm for determining flip angles. Ex. 1009 ¶ 70. This four-step algorithm for determining, or calculating, the flip angles is the only disclosure in the ’182 Application with respect to how the flip angles are selected. *Id.* In addition, the three imaging examples described in the ’182 Application, referred to as Example Nos. 1-3, were each obtained using flip angles calculated using the four-step algorithm to perform the image acquisition. *Id.* However, each Challenged Claim merely requires that “said flip angle is selected to vary” and covers **all** ways of selecting flip angles, whether or not the flip angles are selected using the process described in the ’182 Application. The claimed requirement that the flip angles “vary, among a majority of the total number of said refocusing pulses applied during the echo train, by decreasing to a minimum value and later increasing" is just a **result** of the process used to select flip angles. *Id.* Likewise, obtaining flip angles corresponding to pulse sequence parameters with an effective echo time that is "at least twice" is similarly a **result** of the process used to select the flip angles. *Id.* In addition, the claimed "flip angles **result[ing]** in a reduced power deposition" is just a result of the process used to select the flip angles. *Id.*; Ex. 1001 at cl. 47 (emphasis added).

Claiming only the results of an algorithm while omitting the steps of the algorithm for achieving the results does not comply with the written description requirement. In *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005), the patentee disclosed one algorithm for performing a type of image compression referred to as "a seamless DWT" that included a step of summing DWT coefficients. The Federal Circuit held that claims directed only to the disclosed results of the algorithm that omitted the steps of the algorithm for achieving those results were invalid for lack of written description. *See id.* at 1344:

> The trouble with allowing claim 21 to cover all ways of performing DWT-based compression processes that lead to a seamless DWT is that there is no support for such a broad claim in the specification. **The specification provides only a single way** of creating a seamless DWT, which is by maintaining updated sums of DWT coefficients. **There is no evidence that the specification contemplates a more generic way of creating a seamless array of DWT coefficients**.

(emphasis added). Thus, the Federal Circuit held that "the **description of one method** for creating a seamless DWT **does not entitle the inventor** of the '835 patent **to claim any and all means for achieving that objective**." *Id.* at 1346 (emphasis added). Because the '182 Application describes only one method of selecting flip angles—using the four-step algorithm— but the Challenged Claims cover all methods of selecting flip angles that achieve the claimed results, the Challenged Claims run afoul of exactly the same written description shortcoming that resulted in the invalidation of the claims at issue in *LizardTech*.

The invalid claimed combination at issue in *LizardTech* lacked written description support even though each individual limitation of the claim was adequately described. *See id.* at 1346 (rejecting argument that "section 112 requires only that each individual step in a claimed process be described adequately" because that approach "would lead to sweeping, overbroad claims because it would entitle an inventor to a claim scope far greater than what a person of skill in the art would understand the inventor to possess.") Similarly, even if P.O. could somehow show that each limitation of the Challenged Claims is described in the '182 Application, P.O. cannot show support for its overbroad claims that cover all ways of selecting flip angles—including ways other than the only way described in the '182 Application, the four-step algorithm, and including other ways not yet even conceived. Accordingly, the Challenged Claims lack written description support because each covers a broader invention not disclosed in the ’182 Application.

Likewise, the Challenged Claims lack written description support because the four-step algorithm is the only method provided by the specification for selecting flip angles and a person of ordinary skill would not understand the named inventors of the ’182 Application to have invented an MR pulse sequence that uses flip angles other than those derived according to the four-step algorithm. Ex. 1009 ¶¶ 72-74. *See ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, 558 F.3d 1368, 1377 (Fed. Cir. 2009)(applying *LizardTech* to affirm district court’s grant of summary judgment that claims directed to a “spikeless” or “spike-optional” medical device were invalid for lack of written description because the “specification describes only medical valves with spikes” and “a person of skill in the art would not understand the inventor . . . to have invented a spikeless medical valve.”)

(B) The ’182 Application does not describe the “magnetic-field gradient pulses” limitation recited by each Challenged Claim

Each of the Challenged Claims recites a “a data-acquisition step” that comprises “providing magnetic-field gradient pulses that perform ***at least one of*** encoding spatial information into ***at least one of*** the radio-frequency magnetic resonance signals . . . ***and dephasing transverse magnetization*** . . . .” Ex. 1001 at cls. 75, 140, 157-58, and 176-177 (emphasis added).

First, the ’182 Application does not provide support for the magnetic field gradient pulses encoding spatial information into “at least one of” the RF magnetic resonance signals that follow “at least one of” said refocusing radio-frequency pulses. Ex. 1009 ¶¶ 75-77. The ’182 Application discloses that “[a]ny form of the applied spatial-encoding gradient waveforms . . . are applicable.” Ex. 1014 at 6. However, disclosure of applied spatial-encoding gradient waveforms does not disclose or suggest that spatial information may be encoded into **only one** of the RF magnetic resonance signals for **only one** of the refocusing RF pulses. Ex. 1009 ¶¶ 75-77. The plain meaning of the claimed “at least one” limitation encompasses within its full scope encoding spatial information into **only one** of the RF magnetic resonance signals for **only one** of the refocusing RF pulses. However, a person of ordinary skill in the art would understand that applied spatial-encoding gradient waveforms as disclosed by the ’182 Application necessarily encode spatial information for **all** of the refocusing RF pulses. Ex. 1009 ¶¶ 76-77. In the ’644 IPRs, P.O. appears to acknowledge that encoding spatial information into only one of the RF magnetic resonance signals for only one of the refocusing RF pulses is incompatible with fast spin echo imaging. IPR2016-00357, Paper 21, P.O. Response at 28. However, such hindsight attempts by P.O. to remedy overbroad claims is not a reason to depart from the plain and ordinary meaning of the express language of the Challenged Claims.

Second, the ’182 Application does not describe providing magnetic-field gradient pulses that perform “dephasing transverse magnetization associated with undesired signal pathways to reduce or eliminate contribution of said transverse magnetization to sampled signals.” For example, the ’182 Application does not even mention any of the following words, or equivalents thereof: “dephase,” “dephasing,” “transverse magnetization,” or “undesired signal pathways.” Ex. 1009 ¶ 78. In addition, the figures of the ’182 Application, including Fig. 1, do not necessarily disclose gradient pulses that perform dephasing transverse magnetization associated with undesired signal pathways to reduce or eliminate contribution of said transverse magnetization to sampled signals. *Id.* To the extent any of the many patents and articles that the ’182 Application purports to incorporate by reference disclose gradient pulses that meet the claim limitation, the ’182 Application fails to satisfy the standard to incorporate by reference such subject matter from the patents and articles. “To incorporate material by reference, the host document must identify with **detailed particularity** what specific material it incorporates and **clearly indicate** where that material is found in the various documents.” *See Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378-79 (Fed. Cir. 2007) (emphasis added).

The ’182 Application’s blanket incorporation of 21 references collectively spanning over 1,000 pages and including voluminous treatises provides none of the required particularity on either the specific material incorporated or where that material is found in the references. *See, e.g.*, *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1207 (Fed. Cir. 2013) (holding that a statement in a patent specification that a voluminous technical treatise was “incorporated by reference” in its “entirety” was insufficient to incorporate by reference particular subject matter of the treatise that was not identified with “any detailed particularity.”) In particular, there is no description in the ’182 Application that the subject matter of any of the 21 references to be incorporated related to gradient pulses that dephase transverse magnetization. Ex. 1009 ¶ 80. Accordingly, P.O. cannot rely on cherry-picked disclosures from the 21 references identified by the ’182 Application to provide the missing support for this limitation. Furthermore, articles, being non-patent publications, cannot be incorporated by reference to provide written description support for claimed subject matter. *See* 37 CFR 1.57(c)–(e).

(C) The ’182 Application does not describe the “Effective Echo Time . . . Is At Least Twice” limitation

Each of the Challenged Claims recites a limitation specifying that “**an effective echo time** corresponding to said spin-echo trains . . . **is at least <u>twice</u>**” either “an effective echo time for said turbo-spin-echo or fast-spin-echo spin-echo-train pulse sequence” or “an echo time for said conventional spin-echo pulse sequence." Ex. 1001 at cls. 47, 57, 67, 73, 79, and 80 (emphasis added). These claim limitations compare the effective echo time ("TE_{eff}") of the claimed pulse sequence with either a TE_{eff} of a 180º turbo-spin-echo pulse sequence or the echo time ("TE") of a conventional spin-echo ("SE") pulse sequence. However, the '182 Application does not compare the TE_{eff} of the claimed pulse sequence to the TE_{eff} of a **180º turbo-spin-echo pulse sequence** or the TE of a conventional SE pulse sequence. Ex. 1009 ¶¶ 86-87. The '182 Application instead compares the **contrast** of an image generated using the allegedly inventive pulse sequence to the contrast of an image obtained using a **conventional SE pulse sequence and does not compare the pulse sequence parameters** of the allegedly inventive pulse sequence to the pulse sequence parameters of a conventional SE pulse sequence, at all. Ex. 1014 at 9-10, Figs. 4a-f; Ex. 1009 ¶¶ 85, 88. Although the '182 Application does describe that the TE_{eff} of the allegedly inventive sequence is 328 ms and that the TE of the conventional SE pulse sequence is 80 ms, nowhere does the '182 Application compare the TE_{eff} of the allegedly inventive pulse sequence to the TE_{eff} of any other pulse sequence, much less delineate a range with a boundary of "at least twice" that of any other echo time. Ex. 1009 ¶¶ 88-90. Furthermore, the recited range of "at least twice"—with no upper bound—is problematic on its face. *See, e.g., In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976) (holding claim reciting a range of "at least 35%" invalid under the written description requirement because the claim fails to recite an upper limit, and no upper limit was inherent); *Nissan N. Am., Inc. v. Board of Regents, The Univ. of Texas Sys.*, IPR No. 2012-00037, Paper No. 24 at 11 (P.T.A.B. March 19, 2013) (holding that broad disclosure of a range does not provide written support for a narrower range.) Not only is the unbounded range not disclosed, but it becomes nonsensical as the TE_{eff} of the claimed pulse sequence increases indefinitely. Ex. 1009 ¶ 90.

In *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000), the Federal Circuit held that claims directed to a ratio of two numbers lacked written description support even though the disclosure provides examples from which the ratio could be derived. *See, e.g., id.* at 1328 ("Because the specification does not clearly disclose to the skilled artisan that the inventors of the '360 patent considered the Cmax/C24 ratio to be part of their invention, it is immaterial what range for the Cmax/C24 ratio can be gleaned from the examples when read in light of the claims.") The Federal Circuit explained:

> What the '360 patentees have done is to pick a characteristic possessed by two of their formulations, **a characteristic that is not discussed even in passing in the disclosure**, **and then make it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic**. This is exactly the type of

overreaching the written description requirement was designed to guard against.

Id. at 1327 (emphasis added). Like the claims at issue in *Purdue Pharma*, nowhere does '182 Application disclose that the applicants considered the ratio of effective echo time to a conventional echo time to be part of their invention. Indeed, here there is no evidence that the applicants considered the claimed ratios **at all**. Ex. 1009 ¶ 85. Thus, it is similarly "immaterial" what ranges of this ratio could be gleaned from the example of the '182 Application when read in light of the Challenged Claims.

P.O.'s statements in the '644 IPRs with respect to corresponding limitations of the '644 Patent allege nothing more than the claimed ranges being obvious over the prior art in view of the knowledge of a person skill in the art. Ex. 1009 ¶ 90. However, the knowledge of a person of ordinary skill in the art cannot be substituted for a lack of written description—Section 112 requires **written description**, not a disclosure which renders the claimed inventions obvious. *Lockwood*, 107 F.3d at 1571-72.

C. The Primary Prior Art References

(i) Mugler 2000

Mugler 2000 discloses substantially identical subject matter as that which is disclosed in the '725 Patent. In the '644 IPRs, P.O. only disputes the prior art status of Mugler 2000 but does not dispute that Mugler 2000 anticipates or renders obvious each Challenged Claim.

Mugler 2000 is an abstract presented and published as part of the Proceedings of the International Society for Magnetic Resonance in Medicine, Eighth Meeting, held in Denver on April 1–7, 2000. Ex. 1009 ¶ 115. For example, Mugler 2000 was published on a CD-ROM of the ISMRM proceedings in 2000 as Abstract No. 687. *See* Ex. 1018 at 219 ("Using the ISMRM 2000 CD-ROM"); *id.* at 72 (listing Mugler 2000 as Abstract No. 687); *id.* at 219 ("Click on a session name and the session and its abstracts are displayed."). In addition, the published Mugler 2000 abstract was distributed at least to attendees of the ISMRM proceedings. Ex. 1009 ¶ 115. Accordingly, Mugler 2000 is prior art at least under 35 U.S.C. § 102(b) (pre-AIA) because Mugler 2000 pre-dates by more than one year the effective filing date of the Challenged Claims, which can claim priority no earlier than December 21, 2001, as explained in **V.B.iii**.

Even if the Board finds that the Challenged Claims are entitled to the priority date of the '182 Application, Mugler 2000 still would be prior art to the '725 Patent under 35 U.S.C. § 102(a) (pre-AIA). First, on its face, Mugler 2000 is authored by "another"—Dr. Berthold Kiefer. Dr. Kiefer is an accomplished academic who has been named as an author on numerous other academic research articles, including another paper co-authored with Mugler that extends the research of Mugler 2000. Ex. 1009 ¶ 117 (citing Ex. 1023). In addition, Dr. Kiefer is named as an inventor on 20 U.S. patents, some of which relate directly to the field of the ’725 Patent. For example, Dr. Kiefer is the named inventor of U.S. Patent No. 5,459,401, issued in 1995, which relates to an MRI method for generating T2-weighted images in a turbo-spin echo sequence. Ex. 1025 at Title. Because Dr. Kiefer is a co-author of Mugler 2000, Mugler 2000 is the work of “another.” *See* MPEP § 2132 (“The term ‘others’ in pre-AIA 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be ‘by others.’”).

In addition, Mugler 2000’s April 2000 publication date is before the date of invention in the United States. For example, even if the Board finds that the ’182 Application provides written description support for the claims such that P.O. is entitled to its December 21, 2000 date, in the ’644 IPRs, P.O. has relied on material not found in Mugler 2000—the articles and patents purportedly incorporated by reference—to allegedly provide written description support for several claim elements.[1] Mugler 2000’s April 2000 publication date is before the December 21, 2000 date this material was added to the ’182 Application.

(ii) Alsop

[1] The purported incorporation of this prior art by reference is ineffective, as described in **V.B.iii.B**.

Alsop was published in the Magnetic Resonance in Medicine journal in 1997. *See* Ex. 1004 at 176. Thus, Alsop is prior art to the ’725 Patent at least under 35 U.S.C. § 102(b) (pre-AIA) because Alsop pre-dates by more than one year the earliest possible priority date on the face of the ’725 Patent (Dec. 21, 2000). Alsop relates to extending the echo train duration of a pulse sequence using refocusing pulses with variable flip angles. *See* Ex. 1004 at 176, 179-82; Ex. 1009 ¶ 129. Alsop further relates to “reduce[ing] the power deposition of the sequence dramatically.” Ex. 1004 at 181.

(iii) Mugler 1999

Mugler 1999 is an abstract presented and published as part of the Proceedings of the International Society for Magnetic Resonance in Medicine, Seventh Meeting, held in Philadelphia May 22–28, 1999. Ex. 1009 at ¶ 124. For example, Mugler 1999 was published on a CD-ROM of the ISMRM proceedings in 1999 as Abstract No. 1631. *See, e.g.*, Ex. 1019 at 217 (“Using the ISMRM ’99 CD-ROM”); *id.* at 163 (listing Mugler 1999 as Abstract No. 1631); *id.* at 217 (“Click on a session name and the session and its abstracts are displayed.”). The published Mugler 1999 abstract was distributed at least to attendees of the ISMRM proceedings. Ex. 1009 at ¶ 124. Accordingly, Mugler 1999 is prior art to the ’725 Patent at least under 35 U.S.C. § 102(b) (pre-AIA) because Mugler 1999 pre-dates by more than one year the earliest possible priority date on the face of the ’725 Patent (Dec. 21, 2000).

Like the ’725 Patent, Mugler 1999 discloses a fast-spin-echo imaging technique that permits long echo trains by calculating variable flip angles based on a prescribed signal evolution. *See* Ex. 1003 at Introduction ¶ 2, Materials and Methods ¶ 1. Like the ’725 Patent, Mugler 1999 calculates the flip angles using an iterative process that explicitly incorporates information of a tissue’s relaxation times. *Id.* In particular, Mugler 1999 describes that its “signal-shaping algorithm was based on [the] previously published method” of Mugler et al., “Shaping the Signal Response during the Approach to Steady State in Three-Dimensional Magnetization-Prepared Rapid Gradient-Echo Imaging Using Variable Flip Angles,” Magnetic Resonance in Medicine, Vol. 28, pp. 165-185 (“Mugler 1992”) (Ex. 1020). *See* Ex. 1003 at Materials and Methods ¶ 1. Because Mugler 1999 explicitly identifies the subject matter to be incorporated and where it is found—Mugler 1992’s signal-shaping algorithm—Mugler 1999 provides the detailed particularity required to incorporate the algorithm by reference. *See Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378-79 (Fed. Cir. 2007).

Mugler 1992’s signal-shaping algorithm is a four-step iterative process for determining a flip-angle series that is substantially identical to the four-step iterative flip-angle algorithm disclosed by the ’725 Patent. Ex. 1009 ¶¶ 127-28. In particular, Mugler 1992's four-step algorithm includes: 1) a first step of choosing pulse sequence timing parameters, relaxation parameters, and a target signal intensity; 2) a second step of calculating the flip angle for the *i*th pulse, where *i* ranges from 1 to the number of pulses; 3) a third step of incrementing the flip angle and repeating the calculation; and 4) a fourth step of repeating steps 2) and 3) until a steady state is reached. *Id.* These are the same four steps as the algorithm in the '725 Patent. *Compare* Ex. 1020 at 169 and Ex. 1001 at 10:33-11:14; Ex. 1009 at ¶ 128. Apart from minor modifications to convert Mugler 1992's algorithm from gradient echo imaging to fast spin echo imaging, as indicated by Mugler 1999, the two algorithms are **identical**. *Id.* at ¶ 129. Also, a person of ordinary skill in the art would readily understand how to make these minor modifications to use Mugler 1992's algorithm for fast spin echo imaging. *Id.*

(iv) Mugler Overview

Mugler Overview was published in November of 1999. Ex. 1005 at 1. Accordingly, Mugler Overview is prior art to the '725 Patent under 35 U.S.C. § 102(b) (pre-AIA) because Mugler Overview pre-dates by more than one year the earliest possible priority date on the face of the '725 Patent (Dec. 21, 2000).

Mugler Overview relates generally to pulse sequences used in MR imaging. *See, e.g.*, Ex. 1005 at 661-668. In particular, Mugler Overview relates to MRI techniques using spin-echo pulse sequencess. *See, e.g.*, Ex. 1005 at 668-675.

VI. RELEVANT INFORMATION CONCERNING THE ’725 PATENT

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art for the ’725 Patent is someone with a significant working knowledge of MR spin-echo imaging, especially fast-spin-echo imaging, which is necessarily high in view of the significant knowledge assumed by the ’725 Patent in order to carry out its flip-angle calculation. Ex. 1009 ¶ 92. Such a person would have had a Ph.D. in a physical science (e.g., electrical or biomedical engineering or medical physics) with experience in the development of MR imaging techniques, or an M.D. or M.S. degree in a physical science with significant (3-5 years) work experience in the development of MRI techniques. *Id.*

B. Construction of Terms Used in the Claims

(i) “Substance of interest in said object, with corresponding T1 and T2 relaxation times and a spin density of interest” means “substance in the object having inherent T1 and T2 relaxation times and proton spin density” in this review

This phrase is found in independent claims 47, 57, 67, 73, 79, and 80. P.O. has confirmed its position that selection of T1 and T2 relaxation times or otherwise considering their values is not required in the claims of the ’725 Patent. Specifically, during prosecution of the ’725 Patent, P.O. stated “that none of the independent claims contain any recitation of flip angle or phase calculation, or the selection of T1, T2 or proton density values.” Ex. 1017 at 2. P.O.’s infringement contentions in the GE Litigation confirm this position. Ex. 1021 at 19 (P.O.’s infringement contentions pointing to a relatively dark region of an MR scan to show a "substance of interest . . . having T1 and T2 relaxation times and a spin density.") P.O. has admitted, and for the purposes of this proceeding Petitioner agrees, that the claimed language does not require selection of values for T1 and T2 relaxation times or proton density or otherwise considering these values. Therefore, applying the broadest reasonable interpretation, "substance of interest in said object . . . with corresponding T1 and T2 relaxation times and proton density of interest" means "substance in the object having inherent T1 and T2 relaxation times and proton density."

(ii) "effective echo time" means "the echo time at which the center of k space is sampled" in this review

This phrase is recited in claims 47, 52, 53, 57, 62, 63, 67, 71, 73, 77, 79, and 80 of the '725 Patent. The '725 Patent specifies that "effective echo time" means "the time period from the excitation RF pulse to the collection of data corresponding to substantially zero-spatial frequency (the center of k space)." *Id.* at 3:1-4. However, this definition was added to the '725 specification in an amendment to the specification dated December 12, 2012, during prosecution of the '644 Patent, over 10 years after the filing of the '182 Application . Ex. 1027 at 3. Accordingly, P.O.'s belated definition should be given no weight to establishing the meaning of this term at the time of the priority date of the '725 Patent.

Petitioner submits that the broadest reasonable interpretation of "effective echo time" should include the definition P.O. uses when attempting to prove infringement. In particular, P.O.'s infringement contentions state that for "T2-weighted fast spin echo imaging, **effective echo time as used in the patent equals approximately ½ of the echo-train duration**." Ex. 1022 at 15 (emphasis added). P.O.'s equation is an often-used approximation. Ex. 1009 ¶¶ 102-03. The broadest reasonable interpretation should encompass all of P.O.'s interpretations. Accordingly, "effective echo time" means "the echo time at which the center of k space is sampled." *Id.*

(iii) "echo time . . . value typical in T2-weighted clinical magnetic resonance imaging of the brain" means "an echo time in the range of 60 ms to 130 ms" in this review

This phrase is recited in dependent claims 51-52 and 61-62. There is no definition of "typical" echo time or TE_{eff} in the '725 Patent. Ex. 1009 at ¶ 105. P.O.'s infringement contentions asserts that typical TE_{eff} for T2-weighted imaging include values of 60, 80, 85, 90, and 130 ms. Ex. 1022 at 23-26. Of these, 85, 90, and 130 were for brain. *Id.* The '725 Patent provides one example of an echo time of 80 ms for T2-weighted imaging of the brain using a conventional SE sequence. Ex. 1001 at 13:32-38. A range of TE_{eff} typical for T2-weighted imaging of 60 ms to 130 ms extends to cover each example discussed above and is consistent with the range of TE_{eff} for T2-weighted imaging provided by a leading text. Ex. 1031 at

115-16; Ex. 1009 ¶¶ 106-07. Accordingly, under the broadest reasonable interpretation, "echo time . . . value typical in T2-weighted clinical magnetic resonance imaging of the brain" means "an echo time in the range of 60 ms to 130 ms." *Id.*

(iv) "T2-weighted contrast . . . that is substantially the same" means "T2-weighted contrast that has substantially the same numerical indicator of contrast or that visually appears similar" in this review

This phrase is recited in claims 47, 53, 57, 63, 67, 73, 79, and 80 as part of a limitation specifying that "said signal evolutions . . . result in T2-weighted contrast in the corresponding image(s) that is substantially the same as a T2-weighted contrast that would be provided by imaging said object by using" either "a conventional spin-echo pulse sequence" (Ex. 1001 at cls. 47, 57, and 79) or "a turbo-spin-echo pulse sequence or fast-spin-echo pulse sequence that has constant flip angles, with values of 180 degrees, for the refocusing radio-frequency pulses" (Ex. 1001 at cls. 53, 63, 67, 73, and 80). An objective test to determine the similarity of T2-weighted contrast between two pulse sequences is to calculate a numerical indicator of the T2-weighted contrast each pulse sequence provides. Ex. 1009 ¶ 110. A subjective test would ask a user to look at images and compare whether the contrast appears similar. The '725 Patent suggests such a subjective test is appropriate.

> The very long spin-echo-train images (FIGS. 4B-4F) display ***high contrast*** … , indicating that this echo train shall provide ***clinically useful contrast*** characteristics that ***appear very similar*** to those for conventional T2-weighed SE images . . . .

Ex. 1001 at 13:43-50 (emphasis added). The broadest reasonable construction should encompass both the objective and subjective tests. Accordingly, "T2-weighted contrast . . . that is substantially the same" means "T2-weighted contrast that has substantially the same numerical indicator of contrast or that visually appears similar."

VII. SPECIFIC GROUNDS FOR PETITION

The Challenged Claims are unpatentable for the reasons set forth below. The analysis below compares each claim element to the prior art. P.O. does not dispute that Mugler 2000 discloses the substantially similar claims of the '644 Patent. *See* IPR2016-00357, Paper 7 at 20-39, Paper 21; Ex. 1015. For completeness, Petitioner provides the following analysis on Mugler 2000.

A. Mugler 2000 Anticipates Claims 47-80

(i) Claim 47

(A) "A method of generating a spin-echo-train pulse sequence"

Mugler 2000 is directed to "[s]pin-echo trains used in clinical fast-SE-based imaging." Ex. 1002 at Introduction ¶ 1. In particular, Mugler 2000 discloses a method of generating a fast spin-echo-train pulse sequence. *Id.* at Materials and

Methods ¶¶ 1–2. Mugler 2000 further discloses that the derived pulse sequence was implemented on a "Symphony Siemens Medical Systems" MR imaging apparatus. *Id.*

(B) "providing a data-acquisition step based on said spin-echo-train pulse sequence"

Mugler 2000 discloses a method for generating a fast spin-echo pulse sequence. Ex. 1002 at Materials and Methods ¶¶ 1-2. Mugler 2000 provides an example of a fast-spin-echo pulse sequence calculated according to the disclosed method, which was used to generate images. *Id.* at Fig. 2, Results ¶¶ 1-2. Further, Mugler 2000 discloses a data-acquisition step based on the disclosed spin-echo train pulse sequence because Mugler 2000 discloses a "3D acquisition" performed on the disclosed "very long SE-train." *Id.* at Fig. 2; Ex. 1009 ¶ 133. To the extent not explicitly disclosed, Mugler inherently discloses this limitation by disclosing that an image is generated based on an FSE pulse sequence. Ex. 1009 ¶ 134.

(C) "providing an excitation radio-frequency pulse"

Mugler 2000 discloses that "Figure 1 shows the calculated variable-flip-angle series for the gray matter signal evolution . . . ." Ex. 1002, Results ¶ 1. In particular, Fig. 1 of Mugler 2000 is a graph that shows "flip angle (degrees)" as a function of "refocusing RF-pulse number." *Id.* at Fig. 1. A person of ordinary skill in the art would understand that disclosure of a series of refocusing RF pulses discloses an excitation RF pulse that preceded the refocusing pulses. Ex. 1009 ¶

135. Similarly, Mugler 2000 discloses that its pulse sequence has a "TR" parameter, or repetition time, of 2750 ms, and an "effective echo time" of 328 ms. *Id.* at Fig. 2. Each of these parameters is a time measurement in relation to the time of an excitation pulse. Ex. 1009 at ¶ 135. Further, all FSE sequences inherently has an excitation RF pulse. *Id.* ¶¶ 136-39. Accordingly, Mugler 2000's disclosure of TR and effective echo time parameters discloses the associated excitation pulse. *Id.*

(D) "providing at least two refocusing radio-frequency pulses, each having a flip angle and phase angle"

Mugler 2000 discloses that "Figure 1 shows the calculated variable-flip-angle series for the gray matter signal evolution . . . ." Ex. 1002, Results ¶ 1. In particular, Fig. 1 of Mugler 2000 discloses the flip-angle values for a sequence of 160 refocusing RF pulses, which is "at least two." *Id.* at Fig. 1. Each of the refocusing RF pulses also inherently has a phase angle. Ex. 1009 ¶ 140.

(E) "in order to permit during said data-acquisition step lengthening usable echo-train duration, reducing power deposition and incorporating desired image contrast into the signal evolutions"

First, Mugler 2000 discloses "very long SE trains based on prescribed signal evolutions" that achieved "effective-TEs and echo-train durations of greater than 300 and 600 ms, respectively." Ex. 1002 at Introduction ¶ 3. Second, because each of the flip angles in the pulse sequence illustrated in Fig. 1 of Mugler 2000 is less than 180º, the pulse sequence provides reduced power deposition. Ex. 1009 ¶ 142.

Third, Mugler 2000 explicitly recognizes the achievement of "very long SE-train images (Figs. 2b-f)" having "useful contrast characteristics that appear very similar to those for conventional T2-weighed SE images." Ex. 1002, Results ¶ 2. Because Mugler 2000 discloses each of the three recited features, Mugler 2000 at least discloses "permitting" these features, as discussed above.

(F) "said flip angle is selected to vary, among a majority of the total number of said refocusing pulses applied during the echo train, by decreasing to a minimum value and later increasing"

Mugler 2000 discloses that "Figure 1 shows the calculated variable-flip-angle series for the gray matter signal evolution . . . ." Ex. 1002, Results ¶ 1. In particular, Fig. 1 of Mugler 2000 discloses flip angles that vary among a majority of the refocusing pulses applied during the echo train, which decrease to a minimum and later increase. *Id.;* Ex. 1009 ¶ 145.

(G) "to yield a signal evolution pertaining to the associated train of spin echoes of at least one first substance of interest in said object … and … at least one second substance of interest in said object, with corresponding T1 and T2 relaxation times and a spin density of interest"

Mugler 2000 discloses that "variable flip-angle refocusing RF-pulse series were calculated for several prescribed signal evolutions" "[u]sing a computer-based theoretical model." Ex. 1002, Materials and Methods ¶ 1. Mugler 2000 further discloses that the variable flip angle series was calculated to yield a "signal evolution[]" for the substance of interest of "gray matter." *Id.* All substances, including gray matter, inherently have T1 and T2 relaxation times and spin density. Ex. 1009 ¶ 147. In addition, Mugler 2000's disclosed technique calculates the variable flip angle series "based on prescribed signal evolutions **which explicitly consider the T1s and T2s of interest**." *Id.* at Introduction ¶ 3 (emphasis added). In addition to explicitly disclosing "grey matter" as a substance of interest, the method of Mugler 2000 for selecting flip angles inherently yields a signal evolution for at least one second substance of interest, which inherently has corresponding values of T1 and T2 relaxation times and spin density. *Id.* at ¶ 148. Contrast between light and dark portions of an MR image, as in Fig. 2 of Mugler 2000, requires the presence of at least a first and second substance that each yields a different signal evolution. *Id.*; *see also* Ex. 1021 at 19. Accordingly, Mugler 2000 discloses this limitation. Ex. 1009 ¶¶ 146-48.

(H) "wherein said varying flip angle results in a reduced power deposition compared to the power deposition that would be achieved by using refocusing radio-frequency pulses with constant flip angles of 180 degrees"

The flip angles shown in Fig. 1 of Mugler 2000 reduce power deposition by more than 30% compared to a fast-spin-echo sequence with 180º pulses, as the reduction in power deposition is proportional to the square of the ratio of the reduced flip angle compared to 180º. Ex. 1002 at Fig. 1; Ex. 1009 ¶¶ 142, 149.

(I) "wherein said signal evolutions result in a T2-weighted contrast in the corresponding image(s) that is substantially the same as a T2-weighted contrast that would be provided by imaging said object by using a conventional spin-echo pulse sequence"

Mugler 2000 discloses that its T2-weighted "very long SE-train images (Figs. 2b-f)" generated using the disclosed technique "provide clinically useful ***contrast*** characteristics that ***appear very similar to those for conventional T2-weighed SE images***." Ex. 1002 at Results ¶ 2; *compare id.* at Fig. 2(a) *with id.* at Fig. 2(c). Ex. 1009 ¶ 150.

(J) "wherein an effective echo time corresponding to said spin-echo trains with said signal evolutions of said substances is at least twice an echo time of said conventional spin-echo pulse sequence, and wherein: said effective echo time … is at least on the order of 300 milliseconds; and/or the duration of said spin-echo trains … is at least on the order of 600 milliseconds"

Mugler 2000 discloses the achievement of "T2-weighted . . . imaging of the brain with effective-TEs and echo-train durations of greater than 300 and 600 ms, respectively" and a particular example of 328 ms and 656 ms. Ex. 1002 at Introduction ¶ 3, Fig. 2; Ex. 1009 ¶ 151. Mugler 2000 compares the contrast of such images to those of a conventional SE sequence with echo time 80 ms. *Id.* Accordingly, Mugler 2000's 328 ms TE_{eff} is greater than twice the echo time of 80 ms. Ex. 1002 at Fig. 2; Ex. 1009 ¶ 151. *See, e.g.* Titanium Metals Corp.v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) ("[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if one of them is in the prior art." In addition, Mugler 2000's 328 ms TE_{eff} is "at least on the order of 300 milliseconds" and Mugler 2000's 656 ms duration is "at least on the order of 600 milliseconds." Ex. 1002 at Fig. 2; Ex. 1009 ¶ 151.

(K) "providing magnetic-field gradient pulses that perform at least one of encoding spatial information into at least one of the radio-frequency magnetic resonance signals that follow at least one of said refocusing radio-frequency pulses …"

Mugler 2000 discloses that "[i]n the 3D images, the phase-encoding direction corresponding to the 160-echo train is left-to-right." Ex. 1002 at Fig. 2. A person of ordinary skill in the art would understand that disclosing the applied "phase-encoding direction" discloses the application of magnetic field gradient pulses to encode spatial information. Ex. 1009 ¶ 152. Also, Mugler inherently discloses magnetic-field gradient pulses that encode spatial information into the RF magnetic resonance signals that follow the refocusing RF pulses because Mugler 2000 uses a fast-spin-echo pulse sequence to generate MR images. *Id.* at ¶ 153.

(L) "providing data sampling, associated with magnetic-field gradient pulses that perform spatial encoding"

Mugler 2000 provides an example of a fast-spin-echo pulse sequence, which was used to generate images. Ex. 1002 at Fig. 2, Results ¶¶ 1–2. Further, Mugler 2000 discloses providing data sampling associated with magnetic-field gradient pulses that perform spatial encoding because Mugler 2000 discloses a "3D acquisition" performed on the disclosed "very long SE-train." *Id.* at Fig. 2; Ex. 1009 ¶ 155. Also, Mugler 2000 inherently provides data sampling associated with the magnetic-field gradient pulses that perform spatial encoding because it is not possible to generate an MR image without a data-sampling step. Ex. 1009 ¶ 156.

(M) "repeating said data-acquisition step until . . . has been sampled"

Mugler 2000 discloses that the pulse sequence parameters for its "very long SE-train" pulse sequence were "**TR**/effective TE, **2750**/328 **ms** . . . ." Ex. 1002 at Fig. 2 (emphasis added). This parameter, TR, is referred to as the "repetition time" for a pulse sequence. Ex. 1009 ¶ 157. Mugler 2000's repetition time value of 2,750 ms teaches that a data-acquisition step was repeated every 2,750 ms until sufficient spatial frequency space had been sampled to form an image. *Id.* In addition, P.O.'s infringement contentions confirm that this limitation is met by a fast-spin-echo pulse sequence that has a TR parameter. Ex. 1021 at 26.

(ii) Claim 67

Independent claim 67 recites a method that includes substantially the same claim limitations as the method of claim 47 except that it compares the claimed pulse sequence to a FSE sequence with 180º flip angles rather than a conventional SE sequence. In particular, claim 67 differs from claim 47 in that it: 1) compares the claimed "T2-weighted contrast" to that "provided by imaging said object by using a turbo-spin-echo pulse sequence or fast-spin-echo pulse sequence that has constant flip angles, with values of 180 degrees, for the refocusing radio-frequency pulses" rather than that "provided by imaging said object by using a conventional spin-echo pulse sequence"; 2) compares the claimed "effective echo time" to the "effective echo time of said turbo-spin-echo pulse sequence" rather than the "echo time of said conventional spin-echo pulse sequence," and 3) omits the "effective echo time . . . on the order of 300 milliseconds: and "duration . . .on the order of 600 milliseconds" limitations.

A person of ordinary skill would understand that conventional T2-weighted SE images display substantially the same contrast as a fast-spin-echo image with 180º refocusing pulses if the echo time of the conventional SE pulse sequence matches the effective echo time of the fast-spin-echo pulse sequence. Ex. 1009 ¶ 161. Thus, a person of ordinary skill would understand that Mugler 2000's disclosure of a conventional SE sequence with echo time 80 ms, as discussed in **VII.A.i.I-J**, would have substantially the same contrast as a FSE sequence also having an 80 ms TE_{eff}. *Id.* Also, Mugler 2000's 328 ms TE_{eff} is greater than twice the comparison TE_{eff} of 80 ms. Ex. 1002 at Fig. 2; Ex. 1009 ¶ 161.

(iii) Claims 57 and 73

Independent claims 57 and 73 recite apparatus claims corresponding to method claims 47 and 67, respectively. In particular, the only limitations in apparatus claims 57 and 73 that are not identical to those in method claims 47 and

67, respectively, are six limitations directed to the components of an MR apparatus: "a main magnet system . . . a gradient magnet system . . . a radio-frequency transmitter system . . . a radio-frequency receiver system . . . a reconstruction unit . . . and a control unit . . . ." As shown above, Mugler 2000 discloses the identical limitations of claim 47 and 67 found in claims 57 and 73, respectively. Mugler 2000 discloses that "[i]maging was performed on a 1.5 T whole-body imager (Symphony, Siemens Medical Systems)." Ex. 1002 at Materials and Methods ¶ 2. Thus, Mugler 2000 inherently discloses the apparatus claim elements. Ex. 1009 ¶¶ 163-71. U.S. Patent 6,445,182 ("Dean") (Ex. 1029) provides further evidence of the inherency of these elements. Ex. 1029 at Fig. 3; *see also* Ex. 1009 ¶ 171. Dean describes MRI techniques and scanners for performing the techniques, including MR scanners produced by Siemens. Ex. 1029 at 8:46-49. Dean qualifies as prior art at least under §102(b) because it is based on a PCT publication dated November 4, 1999, which is more than one year prior to the earliest filing date of the '725 Patent. To the extent that the noted elements are deemed to not be inherent, Petitioner asserts that the claims would have been obvious over Mugler 2000 in view of Dean and requests that this Grounds be based on 35 U.S.C. §103. One of skill in the art would have been motivated to combine Mugler 2000 and Dean as both relate to spin echo image sequences. *See* Ex. 1029 at 5:60-65; Ex. 1009 ¶171.

(iv) Claims 79 and 80

Independent claims 79 and 80 recite a "non-transitory computer readable medium having computer program logic that when implemented causes and enables at least one processor" to perform the method of claims 47 and 67, respectively. As shown above, Mugler 2000 discloses the identical limitations of claim 47 and 67 found in claims 79 and 80, respectively. In addition, Mugler 2000 discloses that "[i]maging was performed on a 1.5 T whole-body imager (Symphony, Siemens Medical Systems)." Ex. 1002 at Materials and Methods ¶ 2. Accordingly, Mugler 2000 inherently discloses the computer-readable-medium claim elements. Ex. 1009 ¶ 172. Claims 79 and 80 recite only one additional step not found in claims 47 and 67: "reconstructing an image of the object from data received from said data-acquisition step." Fig. 2 of Mugler 2000 discloses brain images reconstructed from the data received in the data acquisition step. Ex. 1002 at Fig. 2; Ex. 1009 ¶ 173. Accordingly, Mugler 2000 discloses all of the limitations of claims 79 and 80. Ex. 1009 ¶ 173.

(v) Claims 48, 58, 68, and 74

Mugler 2000 discloses "3D imaging of the brain," which samples a three-dimensional volume of spatial frequency space. Ex. 1002 at Introduction ¶ 3; Ex. 1009 ¶ 174.

(vi) Claims 49, 59, 70, and 76

A visual inspection of the flip angles of Fig. 1 of Mugler 2000 show a "decrease, within the first approximately 15% of the total number of echoes, down to a value that is no more than approximately one-third of the initial flip angle." Ex. 1002 at Fig. 1; Ex. 1009 ¶¶ 175-76.

(vii) Claims 50, 60, 69, and 75

Mugler 2000's pulse sequence has 160 refocusing RF pulses, which is greater than 50. Ex. 1002 at Materials and Methods ¶ 1; Ex. 1009 ¶ 177.

(viii) Claims 51, 52, 61, and 62

Mugler 2000's comparison to a conventional spin-echo sequence with an echo time of 80 ms meets the requirements of these claims. Ex. 1002 at Results ¶ 2, Fig. 2. In particular, a conventional spin echo sequence with an echo time of 80 ms, which corresponds to a fast SE sequence with an effective echo time of 80 ms, are values typical in T2-weighted MR imaging of the brain. Ex. 1009 ¶¶ 178-79.

(ix) Claims 53 and 63

For the same reasons discussed above in **VII.A.i.I-J** and **VII.A.ii**, Mugler 2000 discloses these claim limitations. In particular, Mugler 2000 discloses images having substantially the same contrast as a fast-spin-echo sequence having an 80 ms effective echo time, and Mugler 2000's 328 ms TE_{eff} is greater than twice the comparison TE_{eff} of 80 ms. Ex. 1002 at Fig. 2; Ex. 1009 ¶¶ 180-81.

(x) Claims 54, 64, 72, and 78

For the same reasons discussed above in **VII.A.i.H**, the flip angles shown in Fig. 1 of Mugler 2000 reduce power deposition by more than 30% compared to a fast-spin-echo sequence with 180º pulses. Ex. 1002 at Fig. 1; Ex. 1009 ¶ 182.

(xi) Claims 55 and 65

Mugler 2000 discloses a signal amplitude evolution corresponding to "exponential decay for the first 20 echoes (decay constant 114 ms), constant for 66 echoes, and exponential decay for the remaining echoes (decay constant 189 ms); 160 echoes with 4.1ms echo spacing." Ex. 1002 at Materials and Methods ¶ 1. Because Mugler 2000 discloses a 160-echo pulse sequence, the disclosed "decay for the first 20 echoes" occurs within the first 12.5% of the total number of echoes, which is "within the first approximately 20% of the total number of echoes." Ex. 1009 ¶ 186. In addition, because Mugler 2000 discloses a "decay constant 114 ms" for the "exponential decay for the first 20 echoes" in which there was "4.1ms echo spacing," by its 20th echo the prescribed signal amplitude of this example decreased to a value that is approximately 49% of its initial value, which is "no more than approximately two-thirds." *Id.* Further, because Mugler 2000 discloses that the prescribed signal evolution was then "constant for 66 echoes," the prescribed signal amplitude of Mugler 2000 meets the requirement that "the signal amplitude is then substantially constant, up to at least approximately 50% of the total number of echoes." Ex. 1009 ¶ 187.

(xii) Claims 56 and 66

Mugler 2000 discloses "[u]sing a computer-based theoretical model" to calculate the flip angles. Ex. 1002 at Materials and Methods ¶ 1; Ex. 1009 ¶ 188.

(xiii) Claims 71 and 77

As discussed in **VII.A.i.J**, Mugler 2000's 328 ms TE_{eff} is "at least on the order of 300 milliseconds" and Mugler 2000's 656 ms duration is "at least on the order of 600 milliseconds." Ex. 1002 at Fig. 2; Ex. 1009 ¶ 189.

B. Mugler 2000 In View Of Mugler Overview Renders Obvious Claims 47-80

Claims 47-80 are anticipated by Mugler 2000 for the reasons set forth in Section **VII.A** above. To the extent that the Board finds that Mugler 2000 does not inherently disclose one or more of the elements set forth in Section **VII.A**, a person of ordinary skill in the art would have considered claims 47-80 to have been obvious over Mugler 2000 in view of Mugler Overview (Ex. 1005) because Mugler Overview explicitly discloses each inherent claim limitation.

A person of ordinary skill would have considered Mugler 2000 in conjunction with Mugler Overview for several reasons. Ex. 1009 ¶¶ 190-91. For example, Mugler 2000 and Mugler Overview are in the same field of endeavor, as both relate to MRI techniques using fast spin echo pulses sequences. *Id.* Further, the only named author of Mugler Overview is a named author of Mugler 2000, so a person of ordinary skill seeking to learn more about Mugler 2000 would have been motivated to consult the teachings of Mugler Overview. In addition, as its title indicates, Mugler Overview provides a general overview of MR imaging pulse sequences, so a person of ordinary skill in the art would be motivated to use the disclosure of Mugler Overview for background information on any subject matter inherent in and/or not explicitly stated by Mugler 2000. *Id.*

Mugler Overview explicitly discloses each limitation for which inherency was relied in part with respect to Mugler 2000. For example, Mugler Overview explicitly discloses a data-acquisition step on a pulse sequence timing diagram. Ex. 1005 at Fig. 1, 661-662; *see also id.* at Fig. 8, 671-74. Mugler Overview explicitly discloses that pulse sequences have excitation and refocusing pulses. *Id.* at 661. Further, Mugler Overview explains that "[r]adio frequency pulses are often given a qualitative label" of excitation or refocusing "based on their desired effect." *Id.* at 666. For example, pulses that have the purpose of creating transverse magnetization are generally called excitation pulses, and pulses that have the purpose of reversing the phase state of transverse magnetization are generally called refocusing pulses. *Id.* Mugler Overview also teaches that RF pulses have flip angles and phase angles. *Id.* at 684. Mugler Overview also teaches applying gradient pulses that encode spatial information. Ex. 1005 at 661; Ex. 1009 ¶¶ 192-97. Mugler Overview also teaches that a pulse sequence performs data-sampling. Ex. 1005 at Fig. 1, 661; Ex. 1009 ¶¶ 192-97.

C. Alsop In View Of Mugler 1999 Renders Obvious Claims 47-80

Each of the Challenged Claims is anticipated by or rendered obvious in view of Mugler 2000 for the reasons set forth in Sections **VII.A-B**. To the extent that the Board finds that Mugler 2000 does not qualify as prior art or otherwise does not anticipate or render obvious these claims, a person of ordinary skill would have considered the method , apparatus, and computer readable media recited in claims 47-80 to have been obvious over Alsop in view of Mugler 1999.

A person of ordinary skill would also have been motivated to combine Mugler 1999 with Alsop for several reasons. Ex. 1009 ¶¶ 199-201. First, both Alsop and Mugler 1999 address the same problem, *i.e.*, how to extend the echo train duration of an MRI pulse sequence using refocusing pulses with variable flip angles beyond that achievable using traditional refocusing pulses with flip angles of 180º. *Id.* at ¶ 199. For example, for "[a] long train of 180° pulses," Alsop recognizes that "unless all the echoes are acquired within a time on the order of T_2, significant distortion of the point spread function of the image will occur." Ex. 1004 at 176. Mugler 1999 describes this same problem as a blurring problem: for traditional "[t]urbo / fast spin-echo (SE) pulse sequences [that] are widely used for T2-weighted imaging," which have refocusing pulses with flip angle values of 180º, "long echo trains result in substantial image blurring." Ex. 1003 at Introduction ¶ 1; Ex. 1009 ¶ 199.

Second, Alsop and Mugler 1999 disclose substantially the same solution to this problem, namely, using an iterative algorithm to calculate pulse sequences with variable flip angles less than 180° to extend the echo-train duration. Ex. 1009 ¶ 200. For example, Alsop discloses calculating variable flip angles based on "an iterative determination of the flip angle." Ex. 1004 at 178, Fig. 2. Similarly, Mugler 1999 discloses a "variable-flip-angle strategy" in which the "[t]he flip-angle series . . . were derived using a computer-based theoretical model" based on "a previously published method" that uses an iterative algorithm. Ex. 1003 at Introduction ¶ 2, Materials and Methods ¶ 1.

Further, the background of the '725 Patent expressly refers to Alsop as a key prior art reference that "extended" the "concept" of using "low-flip-angle refocusing RF pulses to . . . thereby lengthen its usable duration" to "variable flip-angle series." Ex. 1001 at 3:28-50. Accordingly, a person of ordinary skill would have been motivated to combine the teachings of Mugler 1999 with those of Alsop. Ex. 1009 ¶ 201.

(i) Claim 47

(A) "A method of generating a spin-echo-train pulse sequence"

Alsop is directed to an algorithm for generating a RARE or fast-spin-echo pulse sequence. Ex. 1004 at 176. Alsop further discloses that a pulse sequence derived according to this algorithm was implemented on a GE SIGNA 1.5 Tesla scanner. *Id.* at 180-82.

(B) "providing a data-acquisition step based on said spin-echo-train pulse sequence"

Alsop provides an example of a fast-spin-echo train pulse sequence, which was used to generate images. Ex. 1004 at 180-82. In particular, Alsop discloses that data acquisition occurred when executing the disclosed spin-echo train pulse sequence. *Id.*; Ex. 1009 ¶ 203. In addition, for the same reasons as discussed in **VII.A.i.B** above, Alsop explicitly discloses this limitation, or alternatively, discloses it inherently. Ex. 1009 ¶ 134.

(C) "providing an excitation radio-frequency pulse"

Alsop discloses providing an excitation RF pulse. For example, Alsop discloses a "90° excitation pulse [that] produces a purely transverse magnetization." Ex. 1004 at 177. In addition, Alsop discloses an "excitation pulse" of an "RF pulse train." *Id.* at 178; Ex. 1009 ¶ 204. Also, for the same reasons as discussed in **VII.A.i.C** above, alternatively, Alsop discloses this limitation inherently. Ex. 1009 ¶¶ 136-39, 204.

(D) "providing at least two refocusing radio-frequency pulses, each having a flip angle and phase angle"

Alsop discloses "refocusing flip angle[s]" of an "RF pulse train." Ex. 1004 at 178-79; Ex. 1009 ¶ 205. For example, Alsop discloses an example of providing approximately 20 refocussing RF pulses having the flip angles depicted in Fig. 2. Ex. 1004 at 178; Ex. 1009 ¶ 205. In another example, Alsop discloses a train of refocusing RF pulses of 80 echoes. Ex. 1004 at 180; Ex. 1009 ¶ 205. The number of refocusing RF pulses in each of these examples are "at least two." In addition, each refocusing RF pulse inherently has a flip angle and phase angle, as discussed in **VII.A.i.D**. Ex. 1009 ¶138.

(E) "in order to permit during said data-acquisition step lengthening usable echo-train duration, reducing power deposition and incorporating desired image contrast into the signal evolutions"

First, Alsop recognizes the problem of prior methods "plac[ing] a strong restriction on the length of an echo train," but Alsop discloses that its method could be used for "[l]ong echo-train imaging" with "excellent image quality." Ex. 1004 at 176, 181; Ex. 1009 ¶ 206. Similarly, Alsop discloses that its method provides "more time to acquire signal" compared to conventional "low flip angle RARE." Ex. 1004 at 179; Ex. 1009 ¶ 206. Second, Alsop discloses that its method "reduces the power deposition of the sequence dramatically," providing an example in which 30º flip angles reduce power deposition "by a factor of 36 relative to a 180º train." Ex. 1004 at 181; Ex. 1009 ¶ 207. Third, Alsop discloses that its method demonstrates "excellent image quality" with "expected . . . contrast." For example, Alsop discloses T2-weighted images in Fig. 7 that display desired image contrast.

Ex. 1004 at 182; Ex. 1009 ¶ 208. Because Alsop discloses each of the three recited features, Alsop at least discloses "permitting" these features.

(F) "said flip angle is selected to vary … by decreasing to a minimum value and later increasing"

Alsop discloses an algorithm for selecting flip angles based on an "iterative determination of the flip angle." Ex. 1004 at 178. Applying Alsop's algorithm yields a train of flip angles that vary among a majority of the total number of refocusing pulses as the flip angles asymptotically approach a minimum value, as shown in Fig. 2. *Id.* at 178; Ex. 1009 ¶ 209. However, the flip angles that result from Alsop's algorithm do not increase after reaching the minimum value. *Id.*

It would have been obvious to a person of ordinary skill in the art to use Mugler 1999's iterative algorithm for calculating flip angles instead of the iterative algorithm of Alsop. Ex. 1009 ¶ 210. Alsop's disclosed algorithm does not incorporate T1 and T2 relaxation parameters. *Id.*; Ex. 1001 at 3:38-42 (describing Alsop as "derive[ing] variable flip-angle series . . . when T1 and T2 relaxation are neglected."). However, Alsop recognized that it would be "straightforward to insert T1 and T2 [relaxation] decay into the calculation of echo amplitudes." Ex. 1004 at 179. Mugler 1999's algorithm for calculating flip angles, which is "a function . . . of tissue relaxation times," informs a person of ordinary skill in the art how to take into account T1 and T2 relaxation parameters. Ex. 1003 at Materials and Methods ¶ 1. Thus, a person of ordinary skill in the art would have been motivated to modify Alsop to use Mugler 1999's algorithm for calculating flip in order to take into account the effects of relaxation on the flip angle calculation. Ex. 1009 ¶ 210.

As shown in Fig. 1 of Mugler 1999, using Mugler 1999's algorithm for calculating flip angles produces a series of flip angles that decrease to a minimum and later increase. Ex. 1003 at Results ¶ 2, Fig. 1; Ex. 1009 ¶¶ 211, 213. Unlike the claims at issue in the '644 IPRs, which require "said flip angles then increase for the remaining echoes in said train of spin echoes," claim 47 of the '725 Patent only requires the flip angles to "vary . . . by decreasing to a minimum value and later increasing." Accordingly, whether Mugler 1999's flip angles eventually flatten out at the end of the flip-angle train is irrelevant to whether the disclosed flip angles "decreas[e] to a minimum value and later increas[e]."

Moreover, a person of ordinary skill in the art understands that taking into account relaxation causes the flip angles to rise. Ex. 1009 ¶ 212. For example, Schäffter 1994, which also takes into account relaxation parameters in calculating a flip angle series, shows the calculated flip angles decreasing to a minimum and later increasing. *Id.*; Ex. 2020 at 27, Fig. 1. Accordingly, Alsop in view of Mugler 1999 discloses this limitation.

(G) "to yield a signal evolution pertaining to the associated train of spin echoes of at least one first substance of interest in said object … and … second substance of interest in said object, with corresponding T1 and T2 relaxation times and a spin density of interest"

Alsop discloses yielding a signal evolution pertaining to an associated train of spin echoes of a first and second substance of interest. For example, Fig. 5 of Alsop discloses several signal amplitude evolutions that result from different asymptotic flip angles. Ex. 1004 at 180, Fig. 5; Ex. 1009 ¶ 214. Alsop further discloses brain tissue as the substances of interest. Ex. 1004 at 181-82, Figs. 6-7; Ex. 1009 ¶ 215. In particular, contrast between light and dark portions of an MR image of brain, as in Fig. 7 of Alsop, requires the presence of at least a first and second substance that each yields a different signal evolution. Ex. 1009 at ¶ 147-148. In addition, each of the first and second substances inherently has corresponding values of T1 and T2 relaxation times and spin density. *Id.*

(H) "wherein said varying flip angle results in a reduced power deposition compared to the power deposition that would be achieved by using refocusing radio-frequency pulses with constant flip angles of 180 degrees"

The flip angles shown in Fig. 2 of Alsop reduce power deposition by more than 30% compared to a fast-spin-echo sequence with 180º pulses. Ex. 1004 at 178, Fig. 2; Ex. 1009 at ¶ 149. Furthermore, Alsop discloses an example in which 30º flip angles reduce power deposition "by a factor of 36 relative to a 180º train." Ex. 1004 at 181; Ex. 1009 ¶ 216.

(I) "wherein said signal evolutions result in a T2-weighted contrast in the corresponding image(s) that is substantially the same as a T2-weighted contrast

that would be provided by imaging said object by using a conventional spin-echo pulse sequence"

Alsop discloses "T2-weighted images" that "demonstrat[e] flexibility in selecting T2 contrast." Ex. 1004 at 180. For example, Fig. 7 of Alsop provides T2-weighted images that "demonstrate excellent image quality" with "expected . . . contrast." Ex. 1004 at 181-82, Fig. 7. In particular, the T2-weighted images in Fig. 7 of Alsop have substantially the same T2-weighted contrast as would be provided in a conventional spin-echo pulse sequence having the same echo times. Ex. 1004 at 182; Ex. 1009 ¶ 217. Furthermore, Alsop recognizes that it achieved substantially the same contrast as a fast spin-echo sequence with 180º flip angles: "In summary, the use of a refocusing flip angle other than 180º in RARE sequences can be advantageous for reasons of imaging speed and power deposition **without** severely **affecting** signal-to-noise ratio or **contrast**." Ex. 1004 at 183(emphasis added). As discussed in **VII.A.i.I-J** and **VII.A.ii**, a person of ordinary skill would understand that conventional T2-weighted SE images display substantially the same contrast as a fast-spin-echo image with 180º refocusing pulses if the echo time of the conventional SE pulse sequence matches the effective echo time of the fast-spin-echo pulse sequence. Ex. 1009 at ¶ 217. Thus, Alsop's disclosed T2-weighted contrast would also be substantially the same as that of a conventional spin-echo sequence having the same echo time. *Id.*

Replacing Alsop's algorithm for calculating flip angles with Mugler 1999's algorithm, as described above in **VII.C.i.F**, would not adversely affect contrast. For example, Mugler 1999 similarly discloses that "image contrast is comparable to that for conventional-SE . . . images . . . despite the long echo train length." Ex. 1003, Results ¶ 2; Ex. 1009 at ¶ 218. Accordingly, Alsop, alone or in view of Mugler 1999, discloses this limitation.

(J) "wherein an effective echo time corresponding to said spin-echo trains with said signal evolutions of said substances is at least twice an echo time of said conventional spin-echo pulse sequence, and wherein: said effective echo time … is at least on the order of 300 milliseconds; and/or the duration of said spin-echo trains … is at least on the order of 600 milliseconds"

Alsop discloses a pulse sequence having 82 echoes with 5 ms echo spacing for a duration of 410 ms. Ex. 1004 at 180; Ex. 1009 at ¶ 219. Alsop then teaches that "a 10-ms echo spacing could instead be used," which Alsop encourages to improve the signal to noise ratio. Ex. 1004 at 181; Ex. 1009 at ¶ 219. Accordingly, Alsop discloses an 82-echo pulse sequence, with 10 ms echo spacing. Ex. 1009 at ¶ 219. Multiplying the number of echoes by the echo spacing yields the duration of this pulse sequence, which is 820 ms. *Id.* The 820 ms duration disclosed by Alsop is "at least on the order of 600 milliseconds." *Id.* Furthermore, this sequence would have an effective echo time of approximately 410 ms based on the approximation of half of the duration. *Id.* Further, Alsop produced images in Fig. 7 that have an effective echo time of 157 ms, which would become 314 ms with the suggested change to double the echo spacing to 10 ms. Ex. 1004 at Fig. 7, 180-82; Ex. 1009 ¶ 219. Either of the 410 ms or 314 ms effective echo times are "at least on the order of 300 milliseconds" and "at least twice an echo time of said conventional spin-echo pulse sequence." For example, 410 ms and 314 ms are at least twice the 80 ms example echo time for conventional spin-echo T2-weighted imaging of the brain disclosed in the '725 Patent. Ex. 1001 at 13:34; Ex. 1009 at ¶ 219. In addition, 410 ms is at least twice 100 ms, which UVAPF's expert, Dr. Hennig, has stated as being a typical effective echo time for T2-weighted imaging of brain gray and white matter. '644 IPRs Ex. 2019 ¶ 58. Accordingly, Alsop discloses this limitation. Lastly, Dr. Hennig's opinions in the '644 IPRs regarding written description support for corresponding limitations of the '644 Patent in the '182 Application are incompatible with any conclusion other than Alsop in view of Mugler 1999 rendering this limitation obvious. Ex. 1009 at ¶ 220. In particular, Dr. Hennig has opined that the knowledge of one of skill in the art, Alsop, and the '182 Application's 4-step algorithm for calculating flip angles (which, as explained in **V.C.iii**, is the same as Mugler 1999's 4-step algorithm for calculating flip angles) together shows possession of the "effective echo time . . . at least twice" limitations. *See, e.g.*, '644 IPRs Ex. 2019 ¶¶ 52, 55n9, 65-67, and 72-73; Ex. 1009 at ¶ 220. Written description requires more than a disclosure which renders obvious. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997). Although GE disagrees with Dr. Hennig's opinion that the knowledge of one of ordinary skill in the art, Alsop, and the 4-step flip angle algorithm provides written description support for the "effective echo time . . . at least twice" limitation, GE agrees that the prior art renders this limitation obvious.

(K) "providing magnetic-field gradient pulses that perform … encoding spatial information into at least one of the radio-frequency magnetic resonance signals that follow at least one of said refocusing radio-frequency pulses …"

Alsop discloses a fast-spin-echo pulse sequence to generate MR images. Ex. 1004 at 179-80; Ex. 1009 at ¶ 221. Accordingly, for the same reasons discussed in **VII.A.i.K**, Alsop inherently provides magnetic-field gradient pulses that encode spatial information into at least one of the RF MR signals that follow at least one of the refocusing RF pulses. Ex. 1009 at ¶¶ 153, 221.

(L) "providing data sampling, associated with magnetic-field gradient pulses that perform spatial encoding"

Because Alsop uses a fast-spin-echo pulse sequence to generate MR images, it also inherently provides data sampling associated with the magnetic-field gradient pulses that perform spatial encoding, as discussed in **VII.A.i.L** above. Ex. 1004 at 179-80; Ex. 1009 at ¶¶ 156, 222.

(M) "repeating said data-acquisition step until . . . has been sampled"

Alsop discloses that a "TR" parameter for acquiring images. Ex. 1004 at 180. As explained in **VII.A.i.M**, Alsop's disclosure of a "repetition time" parameter discloses this limitation. Ex. 1009 at ¶¶ 157, 223. Further, Alsop's disclosure with respect to 3D imaging (Ex. 1004 at 182) would require repeating the data acquisition step. Ex. 1009 at ¶ 223. Likewise, Mugler 1999's disclosure of "[p]ulse sequence parameters included: **TR**/TE, **2400**/20 **ms**" similarly discloses this limitation. Ex. 1003 at Results ¶ 3 (emphasis added); Ex. 1009 at ¶ 223.

(ii) Claim 67

As explained above in **VII.A.ii**, claim 67 recites a method that includes substantially the same claim limitations as the method of claim 47 except that it compares the claimed pulse sequence to a FSE sequence with 180º flip angles rather than a conventional SE sequence. As discussed above in **VII.C.i.I**, Alsop discloses that it achieved substantially the same contrast as a FSE sequence with 180º flip angles. In addition, as discussed in **VII.C.i.J**, Alsop's effective echo time of 410 ms or 314 ms and duration of 820 ms satisfies the "at least on the order of 300 milliseconds" and "at least on the order of 600 milliseconds" limitations, respectively. Likewise, for the same reasons as discussed in **VII.C.i.J**, Alsop's effective echo time of 410 ms or 314 ms is "at least twice" the effective echo time of an FSE sequence with 180º flip angles having the same contrast. Ex. 1009 ¶ 224.

(iii) Claims 57 and 73

Alsop discloses that its pulse sequence was "implemented on a clinical GE SIGNA 1.5 Tesla scanner." Ex. 1004 at 180. Accordingly, for the same reasons as discussed above in **VII.A.iii**, the MR scanner disclosed by Alsop inherently discloses each of the apparatus limitations, or such limitations are rendered obvious in view of Dean. Ex. 1009 ¶¶ 163, 165-171, 225.

(iv) Claims 79 and 80

As shown above, Alsop discloses the identical limitations of claim 47 and 67 found in claims 79 and 80, respectively. In addition, Alsop discloses that its pulse sequence was "implemented on a clinical GE SIGNA 1.5 Tesla scanner." Ex. 1004 at 180. Accordingly, Alsop inherently discloses the computer-readable-medium claim elements. Ex. 1009 ¶ 226. Claims 79 and 80 recite only one additional step not found in claims 47 and 67: "reconstructing an image of the object . . ." Fig. 7 of Alsop discloses brain images reconstructed from the data received in the data acquisition step. Ex. 1004 at 182, Fig. 7; Ex. 1009 ¶ 227. Accordingly, claims 79 and 80 are obvious over Alsop in view of Mugler 1999.

(v) Claims 48, 58, 68, and 74

Alsop discloses that its "long echo-train imaging" may be used in "3-dimensional sequences." Ex. 1004 at 182; Ex. 1009 ¶ 228. Likewise, Mugler 1999 discloses "three-dimensional (3D) pulse-sequence structure . . . ." Ex. 1003 at

Introduction ¶ 2; Ex. 1009 ¶ 228. Each of these disclosures samples a three-dimensional volume of spatial frequency space. Ex. 1009 ¶ 228.

(vi) Claims 49, 59, 70, and 76

A visual inspection of the flip angles of Fig. 2 of Alsop show a "decrease, within the first approximately 15% of the total number of echoes, down to a value that is no more than approximately one-third of the initial flip angle." Ex. 1004 at Fig. 2. In particular, Fig. 2 of Alsop illustrates a series of flip angles for approximately 20 echoes. *Id.*The initial flip angle is approximately 125º. *Id.* By the third echo (which is 15% of the 20-echo train), the flip angle has decreased to approximately 35º, which is "no more than one-third of the initial" 125º initial flip angle. *Id.*; Ex. 1009 ¶ 229. Incorporating Mugler 1999's algorithm for calculating flip angles would not change this result, which also shows a decrease in flip angle values that meets this limitation. Ex. 1003 at Fig. 1; Ex. 1009 ¶ 229.

(vii) Claims 50, 60, 69, and 75

Alsop discloses a pulse sequence having 82 refocusing RF pulses, which is greater than 50. Ex. 1004 at 180; Ex. 1009 ¶ 230.

(viii) Claims 51, 52, 61, and 62

As explained in **VI.B.iii**, "effective echo time" or "echo time" that is "typical in T2-weighted clinical magnetic resonance imaging of the brain" means "an effective echo time" or "echo time" that is "in the range of 60 ms to 130 ms." Ex. 1009 at ¶ 231. As discussed in **VII.C.i.J**, Alsop's disclosure of a 410 ms or

314 ms effective echo time and 820 ms duration meets all of the claimed requirements, regardless of which value of "echo time" or "effective echo time" is chosen as typical. For example, each of 410 ms and 314 ms is at least twice the 80 ms example echo time for T2-weighted imaging of the brain and at least twice the 130 ms echo time at the upper end of the range of typical values. Ex. 1009 at ¶ 232.

(ix) Claims 53 and 63

For the same reasons discussed above in **VII.C.i.I-J**, Alsop in view of Mugler 1999 renders obvious these claim limitations. In particular, Alsop discloses a pulse sequence with an effective echo time "at least twice" that of a fast spin echo pulse sequence with 180º flip angles, while resulting in substantially the same T2-weighted contrast. Ex. 1004 at 181-82, Fig. 7; Ex. 1009 at ¶ 233.

(x) Claims 54, 64, 72, and 78

As discussed in **VII.C.i.H**, Alsop discloses an example in which 30º flip angles reduce power deposition "by a factor of 36 relative to a 180º train.". Ex. 1004 at 178, 181, Fig. 2; Ex. 1009 at ¶¶ 216, 234.

(xi) Claims 55 and 65

Fig. 5 of Alsop discloses three signal amplitudes, corresponding to reduced flip angles of 60º, 30º, and 17º, that each decrease, within the first approximately 20% of the total number of echoes, to a value that is no more than approximately two-thirds of the initial value for said signal evolution, and is then substantially constant up to at least approximately 50% of the total number of echoes. Ex. 1004 at 180, Fig. 5; Ex. 1009 ¶¶ 235-36.

(xii) Claims 56 and 66

One of ordinary skill in the art would understand that a computer-based model would be used to calculate the flip angles according to Alsop's iterative algorithm. Ex. 1004 at 178-80; Ex. 1009 ¶ 237. Similarly, Mugler 1999 discloses that "[t]he flip-angle series . . . were derived using **a computer-based theoretical model**." Ex. 1003 at Materials and Methods ¶ 1 (emphasis added).

(xiii) Claims 71 and 77

As discussed in **VII.A.i.J**, Alsop's 410 or 314 ms TE_{eff} are "at least on the order of 300 milliseconds" and Alsop's 820 ms duration is "at least on the order of 600 milliseconds." Ex. 1004 at 180-81; Ex. 1009 ¶ 238.

D. Alsop In View Of Mugler 1999, Further In View Of Mugler Overview Renders Obvious Claims 47-80

To the extent that the Board finds that Alsop in view of Mugler 1999 does not expressly disclose, inherently disclose, or render obvious one or more of the elements set forth in Section **VII.C** above, a person of ordinary skill in the art would have considered any of those claims to have been obvious over Alsop in view of Mugler 1999, further in view of Mugler Overview (Ex. 1005) because Mugler Overview explicitly discloses each inherent claim limitation. *See* Ex. 1009 ¶¶ 192-96. A person of ordinary skill would have been motivated to combine

Alsop and Mugler 1999 with Mugler Overview for each of the same reasons as discussed with respect to considering Mugler 2000 in conjunction with Mugler Overview as discussed in Section **VII.B** above. Ex. 1009 ¶¶ 191, 239.

VIII. CONCLUSION

Petitioner respectfully requests that a Trial be instituted and that the Challenged Claims of the ’725 Patent be canceled as unpatentable.

Attached hereto or included herewith are Powers of Attorney, an Exhibit List, and copies of the references per 37 C.F.R. §§ 42.10(b), 42.63(e), and 42.6(c). Petitioner paid the requisite fee via Deposit Account. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Account No. 50-1529 (Order No. 515998.00889).

Dated: October 19, 2016

Respectfully submitted,

/Marc S. Kaufman, Reg. No. 35,212/
Marc S. Kaufman
Registration No. 35,212
Reed Smith LLP
1301 K Street NW, Suite 1000
Washington, DC 20005-3317

Counsel for Petitioner

CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for *Inter Partes Review*, not inclusive of table of contents, table of authorities, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing, totals no more than 13,997, which is less than the 14,000 allowed under 37 CFR § 42.24(a)(i).

Respectfully submitted,

Date: October 19, 2016 *_/Marc S. Kaufman, Reg. No. 35,212/_*

Marc S. Kaufman
Registration No. 35,212
Attorney for Petitioner

CERTIFICATION OF SERVICE

The undersigned hereby certifies that the above-captioned Petition for *Inter Partes R*eview of U.S. Patent No. *RE45,725*, including its supporting exhibits and Powers of Attorney was served on October 19, 2016 upon the attorneys of record for the patent via Express Mail.

ROBERT DECKER AND RODNEY SPARKS
UNIVERSITY OF VIRGINIA PATENT FOUNDATION
722 Preston Avenue
SUITE 107
CHARLOTTESVILLE VA 22903

Patent Owner's correspondence address of record for U.S. Patent No. RE45,725

Respectfully submitted,

Date: October 19, 2016

/Marc S. Kaufman, Reg. No. 35,212/

Marc S. Kaufman
Registration No. 35,212
Attorney for Petitioner