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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/381,366	08/27/2014	Yoji Ueda	TAN-14-1394	2229

35811 7590 03/15/2019

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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/15/2019	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YOJI UEDA and FUMIO NAKAMURA

Appeal 2018-005971
Application 14/381,366
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to a process for detecting a target nucleic acid. The Examiner rejected the claims as including improper dependent claims, omitting essential subject matter, failing to comply with the enablement and written description requirements, and being directed to patent-ineligible subject matter.[3] We have jurisdiction

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[1] The real party in interest is identified as Toray Industries, Inc. (*see* Br. 1).
[2] We have considered and herein refer to the Specification of Aug. 27, 2014 ("Spec."); Final Office Action of Mar. 23, 2017 ("Final Act."); Appeal Brief of Sept. 6, 2017 ("Br."); and Examiner's Answer of Feb. 6, 2018 ("Ans.").
[3] The Examiner withdrew the rejection of claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 101 for lacking utility (Ans. 36).

under 35 U.S.C. § 6(b). We affirm-in-part and enter a new ground of rejection.

Statement of the Case

Background

"In sandwich hybridization, detection is generally carried out after preliminarily amplifying the sample by a nucleic acid amplification technique such as PCR" (Spec. ¶ 4). However, using PCR may amplify contaminated DNA and requires increasing the number of primers to simultaneously detect a plurality of genes (*see id.*). Detection methods without PCR amplification include sensitization techniques that "require a special enzyme or complex reaction, or special support . . . or special luminous body" (*id.* ¶ 5). Without using nucleic acid amplification or a sensitization technique, "the present inventors discovered that, in sandwich hybridization, a target nucleic acid can be detected with high sensitivity by simultaneously hybridizing a plurality of detection probes that hybridize with different regions in the target nucleic acid" (*id.* ¶ 7).

The Claims

Claims 1–3, 5, 7–13, and 16–20 are on appeal. Independent claim 1 is representative and reads as follows:

> 1. A method of improving sensitivity of detection of a presence or absence of a target nucleic acid comprising:
>
> sequentially or simultaneously bringing
>
> a fragmentation product of a target nucleic acid,
>
> a plurality of detection probes that are complementary to different regions of the target nucleic acid, and

> a capture probe that is complementary to a region of the target nucleic acid and is immobilized on a support,
>
> into contact with each other under hybridizing conditions to hybridize said capture probe with said fragmentation product of said target nucleic acid and to hybridize said fragmentation product with said plurality of detection probes,
>
> thereby binding said plurality of detection probes to said support through said capture probe and said fragmentation product of said target nucleic acid; and

detecting the presence or absence of said plurality of detection probes bound to said support,

wherein a mode of the nucleic acid length of said target nucleic acid or fragmentation product thereof to be hybridized with said capture probe is 100 bases to 1500 bases.

The Issues

A. The Examiner rejected claim 18 under 35 U.S.C. § 112 (pre-AIA), fourth paragraph as being an improper dependent claim (Final Act. 3–4).

B. The Examiner rejected claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 112, second paragraph, for omitting essential subject matter (Final Act. 4).[4]

[4] The Examiner cites to 35 U.S.C. § 112, second paragraph for this rejection, however, failure to recite essential subject matter in the claims is a rejection under 35 U.S.C. § 112, first paragraph. *See In re Mayhew*, 527 F.2d 1229, 1232 (CCPA 1976).

C. The Examiner rejected claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement (*id.* at 5–19).

D. The Examiner rejected claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement (*id.* at 19–30).

E. The Examiner rejected claims 1, 2, and 7 under 35 U.S.C. § 101, as being directed to patent-ineligible subject matter (*id.* at 37–49).

A. 35 U.S.C. § 112, fourth paragraph

The Examiner finds claim 18 is an improper dependent claim for depending from cancelled claim 4 (Final Act. 3–4). Appellants failed to contest the improper dependent claim rejection appeal.

> When the appellant fails to contest a ground of rejection to the Board[,] . . . the Board may treat any argument with respect to that ground of rejection as waived. In the event of such a waiver, the PTO may affirm the rejection of the group of claims that the examiner rejected on that ground without considering the merits of those rejections.

Hyatt v. Dudas, 551 F.3d 1307, 1314 (Fed. Cir. 2008).

In the absence of Appellants' argument on the improper dependent claim, we consider the argument waived and summarily affirm the Examiner's rejection. *See* 37 C.F.R. § 41.37(c)(l)(iv) ("[A]ny arguments or authorities not included in the appeal brief will be refused consideration by the Board for purposes of the present appeal.").

B. 35 U.S.C. § 112, first paragraph (omitting essential matter)

The Examiner finds claim 1 is "incomplete for omitting essential steps, such omission amounting to a gap between the steps" (Final Act. 4). The Examiner finds that "[t]he omitted steps are: a) the generation of fragmentation products of a target nucleic acid; b) the determination of the size of the fragments of the target nucleic acid; and c) the determination of the mode of the length of the target nucleic acid" (*id.*).

We find the Examiner erred. As Appellants correctly point out "the language 'bringing a fragmentation product of a target nucleic acid . . . into contact with [a capture probe and detection probes]' fundamentally implies that the fragmentation product has been generated, either by fragmentation methods or by natural means" (Br. 3–4). Likewise, "one skilled in the art would reasonably understand that the steps of affirmatively determining the size of the fragments and mode of the length of the target nucleic acid are not necessary to detect the presence or absence of the target nucleic acid" (*id.* at 4). Because we do not find any missing elements or steps, we reverse the Examiner's erroneous rejection under 35 U.S.C. § 112, first paragraph for omitting essential subject matter.

C. 35 U.S.C. § 112, scope of enablement

The Examiner finds

> that the claimed method does not require the use of any detectable label. Further, the amended method does not require the removal of detection probes that are bound non-specifically to the solid support prior to performing the detection of said detection probe. It is further noted that the claimed method does not require that the probes bind with any degree of

> specificity for the target, nor exclude the non-specific hybridization of probes to non-target sequences

(Final Act. 7). The Examiner finds:

> In order to practice the full scope of the invention, one would have to determine the nucleotide sequence for each and every organism, much less any gene of interest, in order to identify the correct nucleotide sequences for all target sequences as well as the detection probes and capture probes that are essential to the claimed invention

(*id.* at 13). The Examiner determines "[i]n view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure" (*id.* at 17).

We find the Examiner erred. As Appellants correctly point out:

> Applying the *Wands* factors, the state of the art of molecular biology and the detection of nucleic acids is quite developed, the skill in the art associated with molecular biology and the detection of nucleic acid sequences is quite high (*i.e.*, generally Ph.D. level), and the [S]pecification has a number of working examples (*e.g.*, Examples 1 and 2 showing the claimed method in detecting human papilloma virus and Example 3 showing detection of SNPs)

(Br. 5).

Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the Specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

There can be no reasonable dispute that a person of ordinary skill in the art would be able to detect a target, i.e. known, nucleic acid, by using a

known sandwich hybridization procedure (*see* Spec. ¶ 3) with known capture probes (*see id.* ¶ 32) and detection probes (*see id.* ¶ 39), wherein a mode of the nucleic acid length of said target nucleic acid or fragmentation product thereof (*see id.* ¶¶ 24–25) to be hybridized with said capture probe is 100 bases to 1500 bases (*see id.* ¶¶ 26, 28), following the disclosure of Appellants' Specification.

Therefore, in light of the absence of undue experimentation in performing the method of improving the sensitivity of detection of a nucleic acid, we reverse the Examiner's erroneous enablement rejection.

D. 35 U.S.C. § 112, written description

The Examiner finds "the claimed method fairly encompasses the detection of the millions of bacteria thought to exist as well as the 5676 species of mammals and 32,000 species of fish known to exist, yet not one sequence from any of these animals has been disclosed" (Final Act. 30). The Examiner finds

> [w]hile claim 1 now requires that "a mode of the nucleic acid length of said target nucleic acid or fragmentation product thereof to be hybridized with said capture probe is 100 bases to 1500 bases," no sequence that is 100 bases, much less 1500 bases in length has been disclosed

(*id.* at 26). The Examiner finds that "[t]he aspect that the claims recite the limitation 'target nucleic acid' (claim 1), or that it is 'an animal-derived sample' (claim 8) or even that it is from a human (claim 10) is not considered to satisfy the written description for same" (*id.* at 28).

We find that the Examiner erred. As Appellants correctly point out, "the claims are directed to methods of detecting target sequences using novel methods—not nucleic acid sequences *per se*" (Br. 4). *See Falko-Gunter*

Falkner v. Inglis, 448 F.3d 1357, 1368 (Fed. Cir. 2006) ("[A] requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement.").

> [T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

There can be no reasonable dispute that the method would function with any known target nucleic acid which is subject to fragmentation by known processes (*see* Spec. ¶¶ 24–28) or naturally occurs within the desired length, and is subject to hybridization with appropriately homologous capture and detection probes (*see id.* ¶¶ 31–44).

Therefore, in light of the absence of any unpredictability in performing the generic claim to a method of improving the sensitivity of detection of a nucleic acid, we reverse the Examiner's erroneous written description rejection.

E. 35 U.S.C. § 101, patent eligible subject matter

The Examiner rejected claims 1, 2, and 7 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter (Final Act. 40). In particular, the Examiner finds that the claims "are directed to a combination of natural phenomena- nucleic acids and [their] ability to hybridize to complementary sequences; and a natural relationship- the more detectable probes that bind to a given sequence, the better one is able to detect same (increase sensitivity)" (*id.* at 42).

To determine whether a claim is patent eligible under § 101, we employ the two-step *Alice* framework. In step one, we ask whether the claims are directed to a patent ineligible concept, such as an abstract idea or law of nature. *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 217–18 (2014); *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 75–77 (2012); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015). While method claims are generally eligible subject matter, claims that are directed only to abstract ideas and/or natural phenomena are directed to a patent ineligible concept. *Ariosa*, 788 F .3d at 1376.

Alice Step One

Claim 1 of the instant application is directed to a method of improving the sensitivity of detecting a target nucleic acid immobilized on a support by using a plurality of detection probes complementary to the nucleic acid, and limiting the nucleic acid (or fragments thereof) to a particular size.

Taking up the first step of the patent-eligibility analysis, we note, "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,'" and whether one takes a macroscopic or microscopic view of a claim may be determinative on the issue. *Alice*, 573 U.S. at 217.

Claim 1 is closely analogous to a claim held patent-eligible in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016), which involved producing frozen hepatocytes. *Id.* at 1046.
Just as the claims in *CellzDirect* were "simply not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles" (*id.* at 1048), the instant claims are simply not directed to a natural phenomenon but rather "a new

and useful laboratory technique" (*id.*). We agree with Appellants that the claims are drawn to a "useful laboratory technique, such as a sandwich hybridization method utilizing 'a plurality of detection probes that hybridize with different regions of the target nucleic acid'" (Br. 12). We note that Appellants' position is also consistent with the January 7, 2019 Memorandum, *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50–57 (2019) because these nucleic acid hybridization claims are not directed to any judicial exception such as mathematical concepts, organizing human activities or mental processes but are rather drawn to tangible physical steps that combine target nucleic acids with various nucleic acid probes to detect the presence of a particular target nucleic acid in a sample.

The claimed technique "for producing a tangible and useful result, falls squarely outside those categories of inventions that are 'directed to' patent-ineligible concepts." *CellzDirect*, 827 F.3d at 1050. Therefore, these claims are not directed to a natural phenomenon, and thus, the claims are patent eligible under *Alice* step one. We note that "[i]f the claims are not directed to a patent ineligible concept at step one, we need not address step two of the inquiry." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1134 (Fed. Cir. 2018).

We, therefore, conclude that Supreme Court and Federal Circuit precedent supports the conclusion that the claims on appeal are directed to patent-eligible subject matter.

New Ground of Rejection

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection.[5]

Findings of Fact ("FF")

1. Collins[6] teaches a process of detecting the presence or absence of nucleic acid in an amount below 100 molecules/ml that includes hybridizing a target nucleic acid with a capture probe and a plurality of detection probes (*See* Collins 2979–2980).

2. Figure 1A of Collins is reproduced below:

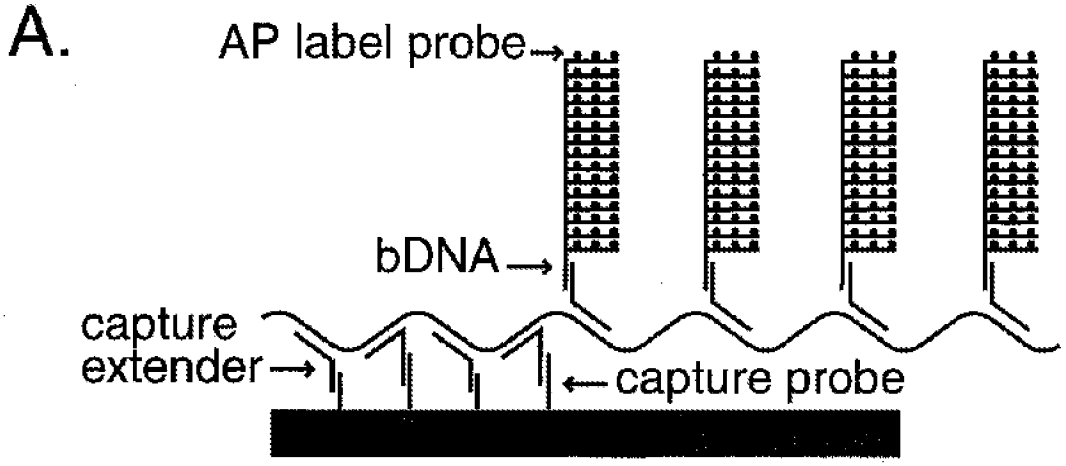

Figure 1, panel A illustrates first generation branched DNA ("bDNA") assay components, including a target sequence, capture probe, and multiple label probes attached to the target sequence (Collins 2980).

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[5] As the Board's function is primarily one of review and not search, we leave to the Examiner the determination of whether the cited prior art, alone or in combination with other well-known and easily identified prior art should be applied to address the remaining dependent claims.

[6] Mark L. Collins et al., *A branched DNA signal amplification assay for quantification of nucleic acid targets below 100 molecules/ml.*, 25 NUCLEIC ACIDS RESEARCH 2979–84 (1997).

3. Liu[7] teaches "[i]n DNA microarray studies, . . . the lengths of nucleic acid molecules are known to affect the rate and efficiency of target-probe duplex formation . . . leading to reduced hybridization efficiencies and false-negative signals. To address this, solutions focusing on target fragmentation . . . have been proposed and demonstrated" (Liu 80).

4. Liu teaches "[p]oor detection sensitivity resulting from low target concentrations is usually remedied by PCR amplification prior to hybridization . . . even though these assays can be affected by the biases associated with enzymatic amplification" (*id.* at 73).

5. Liu teaches "hybridization efficiency and detection sensitivity can be greatly improved by shortening . . . native rRNA targets to smaller sizes. Fragmenting native rRNA targets to 20 to 100 nt by using NaOH-and $ZnCl_2$-catalyzed methods not only enhanced hybridization signal intensities by a factor of 6.1 to 6.2 but also reduced false-negative signals" (*id.* at 80).

6. Liu teaches "enhanced hybridization efficiencies and reduced false-negative signals for DNA fragments when the target length was shortened (Table 1). A reduction in the length of the DNA target from 1,480 bp to approximately 184 to 193 bp could minimize false-negative signals by a factor of 2.4 to 5.6" (*id.* at 81).

7. Liu teaches "extremely short fragments could adversely lead to a slight increase in false-positive signals. Thus, there is a need to compromise between good hybridization efficiencies and hybridization specificities" (*id.*).

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[7] Wen-Tso Liu et al., *Effects of Target Length on the Hybridization Efficiency and Specificity of rRNA-Based Oligonucleotide Microarrays*, 73 APPLIED AND ENVTL. MICROBIOLOGY 73–82 (2007).

8. Small[8] teaches a microarray assay where "hybridization specificity and signal intensity were enhanced using fragmented RNA" suggesting "that it is now possible to apply microarray technology to the direct detection of microorganisms in environmental samples, without using PCR" (Small 4708 (emphasis omitted)).

9. Small teaches:

> Notwithstanding the obvious power and utility of PCR, fundamental uncertainties and errors associated with PCR . . . have significant and mainly negative implications for analysis of, and interpretation of data from, in situ microbial communities and environmental samples. . . . The limitations of PCR . . . in an environmental context therefore extend to any detection method following target amplification, regardless of the sensitivity, specificity, or multiplexed detection capability of the sensor element. By extension, the full power and utility of microarrays to accurately and quantitatively ascribe phenotype and function to in situ microorganisms will therefore be realized only by developing techniques for the direct detection of nucleic acids

(*id.* at 4713–4714).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more

[8] Jack Small et al., *Direct Detection of 16S rRNA in Soil Extracts by Using Oligonucleotide Microarrays*, 67 APPLIED AND ENVTL. MICROBIOLOGY 4708–4716 (2001).

than the predictable use of prior art elements according to their established functions." *Id.* at 417.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

Analysis

Collins teaches a sandwich hybridization method for detecting a target nucleic acid that includes the steps: simultaneously hybridizing a target nucleic acid, a plurality of detection probes that are complementary to different regions of the target nucleic acid, and a capture probe that is complementary to a region of the target nucleic acid and is immobilized on a support; and detecting the presence or absence of the detection probes on the support (FF 1, 2).

Collins does not teach that the target nucleic acid is fragmented before hybridization.

Liu teaches improving the detection sensitivity of sandwich hybridization by using the fragmentation products of target nucleic acids, including DNA fragments of approximately 184 to 193 bp in length, overlapping the 100 to 1,500 bases recited in claim 1 (FF 3–6). Small teaches that a person of ordinary skill would have had reason to use fragmented nucleic acids in order to enhance hybridization specificity and signal intensity in order to avoid PCR induced errors (FF 8–9).

We find that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to use fragment target DNA as taught by Liu and Small in the sandwich hybridization method of Collins because Liu teaches "enhanced hybridization efficiencies and

reduced false-negative signals for DNA fragments" relative to unfragmented target (FF 6) and Small teaches "hybridization specificity and signal intensity were enhanced using fragmented RNA" (FF 8).

We further find it would have been obvious to a person of ordinary skill in the art at the time the invention was made to optimize the nucleic acid target fragment lengths as discussed by Liu and Small because the nucleic acid length taught by Liu overlaps with the claimed nucleic acid length, and because "[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). As taught by Liu, nucleic acid fragment length is a result effective variable for using sandwich hybridization to detect a target nucleic acid, where the fragment should neither be too long nor too short for optimal detection (*see* FF 7). "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

SUMMARY

In summary, we summarily affirm the rejection of claim 18 under 35 U.S.C. § 112 (pre-AIA), fourth paragraph as being an improper dependent claim.

We reverse the rejection of claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 112, first paragraph, omitting essential elements.

We reverse the rejection of claims 1–3, 5, 7–13, and 16–20 under 35 U.S.C. § 112, first paragraph, enablement.

We reverse the rejection of claims 1–3, 5, 7–13, and 16–20 under

35 U.S.C. § 112, first paragraph, written description requirement.

We reverse the rejection of claims 1, 2, and 7 under 35 U.S.C. § 101, patent-ineligible subject matter.

We enter a new ground of rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Collins, Liu, and Small.

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> > (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
> >
> > (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or

> overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

AFFIRMED-IN-PART; 37 C.F.R. § 41.50(b)