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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROBERT TERBRUEGGEN, YENBOU LIU, JOHN RAY CHILDERS JR., CHANG HEE KIM, and MAJID R. ABEDI[1]

Appeal 2016-001717
Application 13/474,596
Technology Center 1600

Before RICHARD J. SMITH, TAWEN CHANG, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods of detecting a plurality of different target nucleic acids in a target sample, which have been rejected as lacking enablement and as indefinite. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellants identify the Real Party in Interest as DxTerity Diagnostics Incorporated. (Appeal Br. 3.)

STATEMENT OF THE CASE

"The detection of specific nucleic acids is an important tool for diagnostic medicine and molecular biology research." (Spec. ¶ 3.) "Ideally, a gene probe assay should be sensitive, specific and easily automatable." (*Id.* ¶ 4.) According to the Specification, "the present invention provides methods and compositions for non-enzymatic chemical ligation reactions which provides rapid target detection and greatly simplified processes of detecting and measuring target nucleic acids." (*Id.* ¶ 10.) Further according to the Specification,

> [a]dvantages of using non-enzymatic approaches for nucleic acid target detection include lower sensitivity to non-natural DNA analog structures, ability to use RNA target sequences and lower cost and greater robustness under varied conditions. In particular, the methods described herein do not require significant sample preparation; that is, the ligation reactions can be performed in the presence of contaminants and buffers that would inhibit or inactivate enzymatic processes for detection. . . . In addition, methods and compositions of the present invention are useful in detection of nucleic acids from samples that are degraded . . . .

(*Id.* ¶ 62.)

Claims 26–30 and 33–44 are on appeal. Claim 26 is illustrative and reproduced below:

> 26. A method of detecting a plurality of different target nucleic acids in a target sample, wherein each target nucleic acid comprises an adjacent first and a second target domain, said method comprising:
> a) providing a reaction mixture comprising said target sample in lysis buffer comprising 2 to 6 molar guanidinium salt
> b) contacting said reaction mixture with a plurality of different probes sets, each probe set comprising:
> i) a first nucleic acid ligation probe comprising:

1) a first probe domain complementary to a first target domain of a target nucleic acid;
2) a first primer sequence; and
3) a 5'-ligation moiety; and

ii) a second nucleic acid ligation probe comprising:

1) a second probe domain complementary to a second target domain of said one target nucleic acid;
2) a second primer sequence; and
3) a 3' ligation moiety;

wherein one of said first or second nucleic acid ligation probes comprises a detectable label and the other comprises one of a binding partner pair;
c) ligating said first and second ligation probes in the absence of a ligase enzyme to form a plurality of different ligation products;
d) contacting said ligation products with a solid support comprising the other of said binding partner pair such that said ligation products are captured on said solid support;
e) washing said solid support;
f) amplifying said different ligation products; and
g) detecting the presence of said ligation products.

(Appeal Br. 29 (Claims App.).)

The Examiner rejects claims 26–30 and 33–44 under 35 U.S.C. § 112(a) or pre-AIA 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. (Ans. 2.)

The Examiner rejects claims 26–30 and 33–44 under 35 U.S.C. § 112(b) or pre-AIA 35 U.S.C. § 112, second paragraph, as being indefinite for omitting essential elements. (Ans. 17.)

I.

Issue

The Examiner has rejected claims 26–30 and 33–44 as failing to comply with the enablement requirement. The Examiner construes "target

nucleic acids" as "encompassing any and all manner of genomic DNA as found in any [life] form" and notes that "the claimed method does not require . . . that the target nucleic acids be known at the time of filing, much less require that any one of the target nucleic acids . . . be that which had utility under 35 [U.S.C. §] 101 at the time of filing." (Ans. 7–8.) The Examiner concludes that the claims are non-enabled because "[t]he state of the art has advanced to the point that certain problems and/or difficulties are known to exist" and because, in light of the breadth of the claims, "[t]he quantity of experimentation necessary is great, on the order of many man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims." (*Id.* at 9–16.) The Examiner further concludes that the claimed methods are either generally inoperable or encompass inoperable embodiments. (*Id.* at 8–9.)

Appellants contend among other things that "the claims are not directed to determining new target sequences" but rather "detection of target sequences using novel methods." (Appeal Br. 16–17.) Appellants contend that practicing the claimed methods does not require undue experimentation, because "[p]robes are designed and made (usually by ordering them from a plethora of available commercial outfits), the standard molecular biology reactions are done, although using novel combinations of reagents, and detection is achieved." (*Id.* at 18–19.) Appellants further dispute the Examiner's contention that the appealed claims are generally inoperable and contend that, to the extent the claims encompass inoperable embodiments, a skilled artisan "could determine which embodiments encompassed by the pending claims would be inoperative or operative with little effort than is normally required in the art." (*Id.* at 19–22.)

The issue with respect to this rejection is whether the preponderance of evidence of record support the Examiner's conclusion that the Specification does not enable the full scope of the claimed inventions.

Analysis

The examiner bears the initial burden of showing that a claimed method is not enabled. *See In re Wright*, 999 F.2d 1557, 1561–62 (Fed. Cir. 1993) ("[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application."). In this case, we find that the Examiner has not established a prima facie case of lack of enablement.

<u>Claim Breadth</u>

The Examiner first contends that "'the target nucleic acids' have been construed as fairly encompassing any and all manner of genomic DNA as found in any [life] form, e.g., any and all bacteria, virus, fungi, mammals, etc." and that this encompasses an enormous amount of DNA. (Ans. 6–8; *see also id.* at 18–19.)

To the extent the Examiner is contending that breadth alone renders the claim non-enabled, we are not persuaded. Although the breadth of the claim is a factor we consider in determining whether a claim is enabled, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling.'" *In re Borkowski*, 422 F.2d 904, 910 (CCPA 1970). The Examiner has emphasized the large number of known virus types and bacteria, fungi, plant, and mammal species (Ans. 7–8); however, the

Examiner has neither provided evidence regarding the level of unpredictability in the art ***relevant to the breadth of the claimed invention***,[2] nor, as we discuss below, persuasively explained how such breadth renders the claims non-enabled.

The Examiner contends that the claimed method does not require the target nucleic acids to be known or to have utility under 35 U.S.C. § 101 at the time of the filing. (Ans. 6–8.) To the extent the Examiner contends that enablement of the full scope of the claim requires all possible target nucleic acids to be sequenced and their utility demonstrated, we are unpersuaded. As Appellants point out, the claims are not directed to particular (or all possible) target nucleic acids, but rather to a general method of detecting whether a target nucleic acid is present in a sample. (Appeal Br. 16.) The invention that must be enabled is the invention defined by the claims. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). Thus, when the claims are not directed to identification of new or all possible target nucleic acids of interest, achieving such a result is not required for the claims to be enabled.

Likewise, although we agree that the claimed methods must have a specific and substantial utility in order for the claims to be enabled, *In re*

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[2] As discussed in more detail below, the Examiner cites two articles to show that the art recognizes certain potential drawbacks to polymerase chain reaction ("PCR"), a particular method of amplification. (Ans. 9–10.) However, the Examiner does not explain how these potential drawbacks render the results of the claimed method unpredictable based on the particular types of target nucleic acids used.

Fisher, 421 F.3d 1365, 1378 (Fed. Cir. 2005), we cannot agree with the Examiner's apparent position that this requires a showing of the utility of all possible target nucleic acids. The Specification states that gene probe assays are useful tools in diagnostic medicine and molecular biology research and that the claimed methods provide some advantages over prior art enzymatic approaches for nucleic acid target detection. (¶¶ 3, 62.) A method that provides advantages over prior art methods used in diagnostic medicine and molecular biology research would seem to satisfy the utility requirement, even if it does not allow immediate detection of, or identify a utility for, all possible target nucleic acids. Put another way, unlike the claim at issue in *Fisher*, which recites expressed sequence tags (ESTs) useful only for conducting experiments on the genes of unknown function of which the ESTs were a part, the claimed methods here are broadly useful for detecting target nucleic acids having particular sequences.

Unpredictability of the Art

The Examiner next contends that "[t]he state of the art has advanced to the point that certain problems and/or difficulties are known to exist." (Ans. 9.) The Examiner points to two references, Thrippleton[3] and Von Töerne,[4] that discuss problems with polymerase chain reaction (PCR), a method of amplifying genomic material such as DNA, presumably because the claims include a step relating to amplification of ligation products. (*Id.* at 5 (construing amplification step to encompass PCR), 9–10.)

As with the Examiner's contention regarding claim breadth, we find that the Examiner has not sufficiently tied the alleged unpredictability in the

[3] Thrippleton et al., US 2013/0040847 A1, published Feb. 14, 2013.
[4] Von Töerne, US 2013/0040843 A1, published Feb. 14, 2013.

art to the claims at issue. For instance, Thrippleton teaches that "[i]ntrinsic problems of PCR lie in its sensitivity and proneness to inhibitors" and that "[i]n PCRs on clinical samples the DNA/RNA is extracted from very crude and extremely variable matrices that frequently harbour polymerase inhibiting components," which may "generate undesirable false negative results." (Ans. 10.) The Examiner does not explain, however, how PCR's sensitivity to inhibitors renders a skilled artisan unable to practice a claim in which amplification is of ligation products bound to a solid support and occurs after washing.

Likewise, Von Töerne teaches that problems with "conventional real-time PCR specific target detection methods" include "[t]he influence of reagent pipetting variations" and variation in quantity due to different instruments or "non-optimal characteristics in the amplification/detection method" such as, e.g., stray light, temperature differences, or differences in the plastic materials holding the sample. (*Id.* (internal quotation marks omitted).) The Examiner does not explain how these potential issues relating to quantification of the target in the sample render a skilled artisan unable to practice a claim that requires detection and not necessarily quantification.

In short, we find that the Examiner has not shown by a preponderance of evidence that the potential problems of PCR discussed in Thrippleton and Von Töerne render a skilled artisan unable to perform the amplification step recited in the claims.[5]

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[5] The Examiner also notes without further explanation that another "aspect of unpredictability" is that "the length of the probe can and does affect the specificity of the interaction of [the] probe with [the] target." (Ans. 11.) The Examiner points to statements in the Specification in support of this

Quantity of Experimentation

The Examiner contends that "[t]he quantity of experimentation necessary is great, on the order of many man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims." (Ans. 10; *see also id.* at 20.)

The Examiner first contends that, "[i]n order to practice the full scope of the invention, one would have to first determine the nucleotide sequence for each and every organism, much less any gene of interest, before one would be able to select appropriate probe and/or primer sequences that are essential to the claimed invention." (*Id.* at 11.) As we have already discussed above, the claims are not directed towards identification of new or all possible target nucleic acids of interest but rather a general method of whether any particular target nucleic acid is present in the sample. Thus, we disagree with the Examiner that a skilled artisan would need to *a priori* determine the nucleotide sequence for each and every organism or gene of interest in order to practice the full scope of the invention.[6]

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statement. (*Id.*) The Examiner has cited no evidence or persuasively shown that a skilled artisan would not be able to design a probe having a length that ensures sufficient specificity in the probe/target interaction to practice the claimed invention.

[6] The Examiner cites as support for his position *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013). (Ans. 13.) Although we agree with the general statements of law from *Wyeth* cited by the Examiner, the facts of *Wyeth* render it inapposite. The claim at issue in *Wyeth* recites "a method of treating or preventing 'restenosis in a mammal . . . which comprises administering an antirestenosis effective amount of rapamycin to said mammal." *Wyeth*, 720 F.3d at 1382. The *Wyeth* Court found that "there is no genuine dispute that practicing the full scope of the claims would require synthesizing and screening *each* of at least tens of thousands of compounds." *Id.* at 1385. In this case, because the claim does not require

The Examiner also contends that, "[a]s presently worded, the claimed method fairly encompasses use of multiplex detection of short tandem repeat (STR) loci at issue in *Promega Corp. v. Life Techs Corp.*," 773 F.3d 1388 (Fed. Cir. 2014) (reversed and remanded by *Life Tech Corp. v. Promega Corp.*, 137 S.Ct. 734 (2017) on other grounds), which our reviewing court found to be non-enabled. (Ans. 13; *see also id.* at 21.)

The claim at issue in *Promega* recites "[a] kit for simultaneously analyzing short tandem repeat sequences in a set of short tandem repeat loci from one or more DNA samples, comprising: A single container containing oligonucleotide primers for each locus in *a set of* short tandem repeat *loci* which can be co-amplified, *comprising* HUMCSF1PO, HUMTPOX, and HUMTH01." *Id.* at 1343. The *Promega* Court found that, "[i]n this field of technology, introducing even a single [short tandem repeat (STR)] locus to an existing loci multiplex significantly alters the chemistry of, and has an

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the target nucleic acid to perform any particular function, and because the Examiner has not persuasively shown that whether the claimed method would work is dependent on the specific structure (i.e., sequence) of the target nucleic acid, we do not agree that practicing the full scope of the claims would require sequencing and testing all potential target nucleic acids. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991), which is cited in the portion of *Wyeth* relied upon by the Examiner, is inapposite for similar reasons. Specifically, the claims at issue in *Vaeck* are directed towards a chimeric gene capable of being expressed in Cyanobacterial cells. *Id.* at 490. In that case, however, it was found that the molecular biology of Cyanobacteria had only recently become the subject of intensive investigation, which is also limited to a few genera, and that the level of unpredictability regarding heterologous gene expression in Cyanobacteria as a group is thus high. *Id.* at 493. Here, again, the Examiner has failed to show that the practice of the claimed method would unpredictably depend on the particular type or sequence of the target nucleic acid.

unpredictable effect on, whether the resulting multiplex will successfully co-amplify." *Id.* at 1346.

The Examiner contends that,

> [w]hile the issue in *Promega* dealt with the enablement of the full scope of primers to be used in amplification, the claimed method presents issues of enablement directed at not only the primer, which is a component of the 'nucleic acid ligation probe[s]', but also the means used to effect ligation, for as required in Claim 26, step c), one is required to effect 'ligating said first and second ligation probes <u>in the absence of a ligase enzyme</u> to form a plurality of different ligation products' (emphasis added). While the first and second 'nucleic acid ligation probes' are to hybridize to a first and second target domain, the 'target domain[s]' can be of any size. Further, there is no requirement that the first and second ligation probes actually hybridize immediately adjacent to one another such that ligation could possibly occur.

(Ans. at 14–15.)

We are not persuaded that the Examiner has established that the same enablement analysis applies to the claims at issue in *Promega* and the claims on appeal. For instance, the unpredictability discussed in *Promega* relates to co-amplification of multiple STR loci, whereas the amplification required in the claims relates to amplification of ligation products. In any event, assuming that the Examiner is correct that the claimed method encompasses co-amplification of STRs as described in *Promega*, we are not persuaded that the Examiner's citation to *Promega*, without more, suffices to establish a prima facie case of non-enablement. As Appellants point out, the priority dates of *Promega* patents and the application on appeal differ, and the Examiner has not cited evidence or argued that the state of the art has remained the same. (Reply Br. 4.)

As discussed above, the Examiner also contends that Appellants have not enabled the full scope of "'ligating said first and second ligation probes in the absence of a ligase enzyme to form a plurality of different ligation products.'" (Ans. 14–15 (internal quotation marks omitted).) In particular, the Examiner contends that the Specification states that the identification of litigation moieties recited in the claims "depends on the chemistry of the ligation to be used" and that,

> [a]s presently worded, the claimed method fairly encompasses any future devised means that would allow for the requisite ligation of the first and second nucleic acid ligation probes as the claimed method is not limited to any particular "chemistry" and, thus[], fairly "cover[s] potentially thousands of undisclosed embodiments in an unpredictable field."

(*Id.* at 15.) The Examiner further responds to Appellants' argument as follows:

> [N]either the disclosure nor the Brief has been found to teach in detail how any and all manner of first and second probes in an infinite number of "different probe sets" are to be ligated "in the absence of a ligase enzyme." While ligation between probes via use of a ligase is well developed in the art, the aspect of ligating probes "in the absence of a ligase enzyme" is highly unpredictable.

(*Id.* at 21.)

Although we appreciate the Examiner's position, we note that negative limitations, such as a limitation excluding the use of ligation enzyme, are not per se impermissible. *Cf. Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012) (stating that "[n]egative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation"). The Specification teaches several "non-enzymatic or template mediated chemical ligation methods"

that may be used in the claimed invention, including, e.g., use of nucleophile ligation moieties. (*See, e.g.*, Spec. ¶¶ 117, 146–148.) On the other hand, the Examiner has not cited any reason or evidence to support his contention that, "[w]hile ligation between probes via use of a ligase is well developed in the art, the aspect of ligating probes 'in the absence of a ligase enzyme' is highly unpredictable." (Ans. 21.) In light of the lack of evidence regarding the predictability of ligation in the absence of a ligase enzyme, we find that the Examiner has not sufficiently established a prima facie case that the claims are not enabled as to the limitation of "ligating said first and second ligation probes in the absence of a ligase."[7] *See Wright*, 999 F.2d at 1561–62 ("When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.") (citation omitted).

[7] Likewise, although the Examiner argues that the claims on appeal present "issues of enablement directed at . . . the primer, which is a component of the 'nucleic acid ligation probe[s],'" and emphasizes that "the 'target domain[s]' can be of any size," the Examiner does not provide persuasive evidence or arguments regarding ***how*** either inclusion of primers in the ligation probes or the size of the target domains render the claims on appeal non-enabled, other than by reference to *Promega*. (Ans. 14–15.) As already discussed, we do not find the reference to *Promega* without more to establish a prima facie case of non-enablement.

Inoperable Embodiments

The Examiner also contends that the claims on appeal are not enabled because they are inoperable and/or include inoperable embodiments.

The Examiner first contends that, although the claimed method requires "the production of 'a plurality of different ligation products,'" the claim describes only "a first nucleic acid ligation probe" and "a second nucleic acid ligation probe," which can only form one ligation product. (Ans. 8–9.)

We are not persuaded. The claims require "a plurality of different probe sets," with each probe set comprising a first and a second nucleic acid ligation probe." (Appeal Br. 29 (Claims App.).) The ligation of the first and second ligation probes from the plurality of different probe sets would result in a plurality of different ligation products.

In a similar vein, the Examiner contends that the claim requires performing the "step of 'detecting the presence of ligation products'" without requiring that "the products have a size and[/]or label that is distinguishable from any and all other ligated probes that are directed to any other member of the 'plurality of different target nucleic acids in a target sample.'" (Ans. 15–16.) The Examiner contends that "[s]imply detecting any 'ligation products' which is/are indistinguishable from that for any other member of the 'plurality of different target nucleic acids' would not allow one to determine whether or not one has actually detected 'a plurality of different target nucleic acids in a target sample' or just one." (*Id.* at 16; *see also id.* at 19–20.)

We are not persuaded. The Specification teaches using "detectable labels to aid in the identification . . . of the ligated oligonucleotide product,

including, for example, . . . optical[] and electrochemical labels [or] variable spacer sequences or 'size tags' comprising nucleic acid sequences that are sized to be specific for a particular target." (Spec. ¶ 60.) The Examiner does not explain why such disclosures in the Specification would not enable a skilled artisan to select different detectable labels that allows identification of a plurality of different target nucleic acids in a target sample.[8]

The Examiner contends that the claimed method is further inoperable because "[t]he claim language does not preclude the first and second ligation probes being parts of a common oligonucleotide that hybridizes to adjacent target nucleic acid sequences therein allowing for ligation (circularization) of the oligonucleotide." (Ans. 6–7 (explaining that "Applicant . . . teaches that the first and second probes may actually be opposite ends of but a single oligonucleotide"), 9.) The Examiner contends that, "[a]ccordingly, any and all sequences present in a linear form would also be present in the ligated form," and "there [would be] no change in amount of detectable label[] whether or not any hybridization ever occurred, much less any ligation." (*Id.*)

As we understand it, the Examiner's contention is that, to the extent the first and second ligation probes constitute two ends of a single oligonucleotide, and where one probe comprises a detectable label and the other comprises one of a binding partner pair, the oligonucleotide when

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[8] The Examiner appears to believe that enablement requires the ***claim*** to contain all of the information necessary to make and use the claim. It is the ***Specification***, however, that must enable the claims. *Wright*, 999 F.2d at 1561 ("[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'") (citations omitted).

contacted with "a solid support comprising the other of said binding partner pair" will be captured on the solid support and be detected regardless of whether hybridization or ligation has taken place. The Examiner also appears to argue first and second litigation probes located on two ends of the same oligonucleotide will necessarily be ligated and the oligonucleotide circularized.

We are not persuaded that the Examiner has established a prima facie case that the ***Specification*** does not enable a skilled artisan to practice the claimed invention because the ***claims*** do not specifically exclude the first and second probes from being on same oligonucleotide. For instance, the Specification states:

> It should be noted that the "upstream" and "downstream" oligonucleotides can, optionally, constitute the two ends of a single oligonucleotide, in which event ligation yields a circular ligation product. The binding regions on the 5' and 3' ends of the linear precursor oligonucleotide must be linked by a number of intervening nucleotides sufficient to allow binding of the 5' and 3' binding regions to the polynucleotide target.

(Spec. ¶ 129.) The Examiner provides no evidence or persuasive argument that the 5' and 3' ends of the linear precursor comprising the upstream and downstream oligonucleotides (i.e., the first and second ligation probes) would automatically ligate to each other given the teaching that they must be linked by a number of intervening nucleotides sufficient to allow binding to the polynucleotide target and thus presumably not located in immediate proximity to each other.

Likewise, the Examiner provides no evidence or persuasive argument that a skilled artisan would not be able to choose (1) a form of the first and second ligation probes and (2) a means of detection that would permit

detection of the ligation probes only when hybridization to the polynucleotide target has occurred.

The Examiner also contends that,

> [a]s presently worded, there is no requirement that the probes hybridize such that the 3' and 5' ligation moieties are adjacent to one another such that ligation could occur. In support of this interpretation, attention is directed to paragraph [0120], which teaches that in addition to using two ligation probes, one may opt to use "more than two ligation probes" when additional specificity is desired. Absent means and proper orientation, it stands to reason that ligation would not spontaneously occur. In short, the method would be inoperable.

(Ans. 15.)

We are not persuaded. The Examiner once again appears to believe, erroneously, that the claims themselves (rather than the Specification) must set forth all the information that allows a skilled artisan to practice the claimed invention. In this case, the Specification teaches that

> [l]igation probes of the invention are designed such that when the probes bind to a part of the target polynucleotide in close spatial proximity, a chemical ligation reaction occurs between the probes. In general, the probes comprise chemically reactive moieties (herein generally referred to as "ligation moieties") and bind to the target polynucleotide in a particular orientation, such that the chemically reactive moieties come into close spatial proximity, thus resulting in a spontaneous ligation reaction that can take place without the use of a ligase enzyme.

(Spec. ¶ 109.) The Examiner has not explained or provided persuasive evidence why, in light of such disclosure, a skilled artisan would not be able to design ligation probes that would allow ligation to spontaneously occur without undue experimentation. *Cf. Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576–77 (Fed. Cir. 1984) (explaining that "it is not a function of the claims to specifically exclude . . . possible

inoperative substances . . . " and stating that claims are not necessarily invalid for including inoperative embodiments absent a showing that such inoperative embodiments "in effect forces one or ordinary skill in the art to experiment unduly in order to practice the claimed invention") (internal quotation marks and citations omitted).

Finally, the Examiner discounts Appellants' contention that a skilled artisan "could determine which embodiments encompassed by the pending claims would be inoperative or operative with little effort than is normally required in the art," finding the contention to be attorney argument rather than evidence. (Ans. 20 (internal quotation marks omitted).) Although we agree that attorney arguments are no substitute for evidence, *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989), we are also cognizant that the Examiner bears the initial burden of showing that a claimed method is not enabled. *Wright*, 999 F.2d at 1561–62. As discussed above, we find that the Examiner has not sufficiently articulated a reasonable explanation as to why the claims on appeal are not adequately enabled ***by the Specification*** and, thus, has not established a prima facie case of non-enablement.

Accordingly, we reverse the Examiner's rejection of claims 26–30 and 33–44 as lacking enablement.

II.

Issue

The Examiner has rejected claims 26–30 and 33–44 as indefinite. The Examiner finds that the claims are "incomplete for omitting [the] essential elements" of "[m]eans of effecting the ligation" and "[m]eans for detecting the 'detectable label.'" (Ans. 17.) In response to the Appeal Brief, the Examiner further clarifies that the metes and bounds of the claimed methods

cannot be readily determined because (1) the Specification explains that "the ligation moiety depends upon the chemistry to be used" but "[t]he claimed method does not specify the chemistry used, much less specify if the ligation is to be 'spontaneous' and/or whether any linker is to be used" and (2) "in order to practice the claimed method, use of some means (elements) for 'detecting the presence of said ligation products' is both required and is not recited." (*Id.* at 22–23.)

Appellants contend that a skilled artisan "would recognize that ligation spontaneously occurs between the 5'- and 3'- ligation moieties" and further "would understand how to identify a detection method, depending on the particular detectable label used," including for instance the methods of detecting a detectable label set forth in the Specification. (Appeal Br. 27; *see also* Reply Br. 6–8.)

We find the Examiner has not established a prima facie case that the claims are indefinite. "The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification." *Union Pacific Resources Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001). The gravamen of the Examiner's rejection, however, appears to be that the claims are too broad. That is, the Examiner has not contended that a skilled artisan would not understand what is meant by "ligating the first and second ligation probes," "a ligase enzyme," or "detecting the presence of . . . ligation products" in light of the Specification; rather, the Examiner's complaint is that the claims should have further specified particular means of ligation and detection. However, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971).

Accordingly, we reverse the Examiner's rejection of claims 26–30 and 33–44 as indefinite.

SUMMARY

For the reasons above, we reverse the Examiner's decision rejecting claims 26–30 and 33–44.

REVERSED