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Paper 25
Entered: 3 September 2013

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS
Petitioner,

v.

ISIS INNOVATION LIMITED
Patent Owner.

Case IPR2013-000250 (LMG)
Patent 6,258,540

Before LORA M. GREEN, FRANCISCO C. PRATS, and JEFFREY B. ROBERTSON, Administrative Patent Judges.

GREEN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. BACKGROUND

Ariosa Diagnostics ("Ariosa") filed a petition ("Pet.") requesting *inter partes* review of claims 3, 8, 12, 13, 15, and 18 of U.S. Patent No. 6,258,540 (the "'540 patent"; Ex. 1001) on April 19, 2013. (Paper 1.) Patent Owner, Isis Innovation Limited ("Isis"), filed a Preliminary Patent Owner Response on June 10, 2013. (Paper 10.) We have jurisdiction under 35 U.S.C. §§ 6(b) and 314.

The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which states:

> THRESHOLD. -- The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Inter partes review is instituted only if the petition supporting the ground demonstrates "that there is a reasonable likelihood that at least one of the claims challenged in the petition is unpatentable." 37 C.F.R. § 42.108(c). In making that determination, the Board considers both the Petition and the Preliminary Response of the Patent Owner. *Id.*

We conclude that Ariosa has shown that there is a reasonable likelihood it will prevail with respect to at least one of the challenged claims, and we thus grant the petition as to claims 3, 8, 12, 13, 15, and 18.

A. Related Proceedings

The '540 patent is asserted in co-pending litigation captioned as *Ariosa Diagnostics v. Sequenom et al.*, N.D. Cal., Case No. 3:11-cv-06391 (Pet. 3). The

'540 patent is also the subject of Appeal No. 12-1531 before the Court of Appeals for the Federal Circuit in *Aria Diagnostics, Inc. v. Sequenom, Inc.* (Paper 9 at 1).

This *inter partes* review is related to IPR2012-00022, requesting review of claims 1, 2, 4, 5, 8, 19-22, 24, and 25 of the same patent. In that proceeding, review was instituted as to claims 1, 2, 4, 5, 8, 19-22, 24, and 25. *See* IPR2012-00022, Paper 24. That decision is incorporated and adopted herein by reference.[1]

B. Standing

Isis renews its argument made in IPR2012-00022, that 35 U.S.C. § 315(a)(1) forbids instituting *inter partes* review, because Ariosa filed a civil action seeking a declaratory judgment of noninfringement (Prelim. Res. 48-49). We are not persuaded by Ariosa's argument for the reasons expressed in Paper 20 of IPR2012-00022.

Isis contends further that, under 35 U.S.C. § 315(b), the "Office may not institute *inter partes* review if the petitioner filed its petition more than one year after being served with a complaint alleging infringement of the patent" (Prelim. Res. 42). According to Isis, Aria Diagnostics, Inc., now Ariosa, accepted service of a complaint alleging infringement of the '540 patent, more than a year before the petition filing date of April 19, 2013 (*id.*).

Isis acknowledges that the parties later agreed to dismissal of the civil action without prejudice (*id.*). Isis argues, however, that § 315(b) leaves no room for discretion, as it states that "*inter partes* review 'may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner . . . is served with [the] complaint'" (*id.* (alteration in original)).

[1] We exercise our discretion to simplify the instant decision. The parties, however, are not authorized to use incorporation by references. 37 C.F.R. § 42.6(a)(3).

According to Isis, the fact that the infringement suit was dismissed without prejudice is immaterial to whether or not Ariosa is barred from bringing the instant *inter partes* review against Isis (*id.* at 42-44).

That argument already has been considered by the Board in *Macauto U.S.C.* v. *BOS GMBH &KG*, IPR2012-00004. In that proceeding, the Board noted that the bar against filing an *inter partes* review under 35 U.S.C. § 315(b) did not attach to a complaint of infringement that voluntarily was dismissed without prejudice. *See* IPR2012-00004, Paper 18 at 14-16. We, thus, hold that Ariosa is not barred under 35 U.S.C. § 315(b) from filing the instant petition against Isis. As a result, we need not address Isis' arguments (Prelim. Res. 44-46) regarding joinder in the context of the bar under § 315(b).

C. The '540 Patent

We refer to the decision instituting review in IPR2012-00022, Paper 24, for a discussion of the '540 patent.

D. Representative Claims

We refer to the decision instituting review in IPR2012-00022, Paper 24, for a discussion of representative independent claims of the '540 patent.

Dependent claims 3, 12, 13, 15, and 18, all either depend directly or ultimately on independent claim 1. Claim 3 adds the limitation of fetal specific primers, and claim 12 adds the limitation of determining the sex of the fetus. Claim 13 requires determination of the concentration of fetal nucleic acid in the maternal serum or plasma, and claim 15 is drawn to the detection of a maternal or fetal condition in which the level of fetal DNA in the maternal serum or plasma is

higher or lower than normal. Claim 18 is drawn to the detection of an aneuploidy based on the concentration of fetal nucleic acid.

E. Prior Art Relied Upon

The prior art references relied upon Ariosa are:

Lo et al. ("Lo 1997"), *Presence of fetal DNA in maternal plasma and serum*, 350 LANCET 485-487 (1997) (Ex. 1016).

Simpson et al. ("Simpson"), *Isolating Fetal Cells in Maternal Circulation for Prenatal Diagnosis*, 14 PRENATAL DIAGNOSIS 1229-1242 (1994) (Ex. 1025).

Kazakov et al. ("Kazakov"), *Extracellular DNA in the Blood of Pregnant Women*, 37(3) CYTOLOGY (TSITOLOGIA) 232-236 (1995) (Ex. 1014).

Schallhammer et al. ("Schallhammer'), *Phenotypic comparison of natural killer cells from peripheral blood and from early pregnancy decidua*, 3 EARLY PREGNANCY: BIOLOGY AND MEDICINE 15-22 (1997) (Ex. 1022).

Bianchi et al. ("Bianchi"), *Fetal Cells in Maternal Blood: Determination of purity and Yield by Quantitative Polymerase Chain Reaction*, 171 AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 922-26 (1994) (Ex. 1043).

Mutter et al. ("Mutter'), *Molecular diagnosis of sex chromosome aneuploidy using quantitative PCR*, 19 NUCLEIC ACIDS RESEARCH 4203-07 (1991) (Ex. 1048).

Lo et al. ("Lo 1990"), *Detection of single-copy fetal DNA sequence from maternal blood*, 335 LANCET 1463-64 (1990) (Ex. 1044).

Lo et al. ("Lo 1989"), *Prenatal sex determination by DNA amplification from maternal peripheral blood*, LANCET 1363-65 (1989) (Ex. 1045).

F. The Asserted Challenges

The challenges presented by Ariosa are presented below (Pet. 24-54).

Reference(s)	**Basis**	**Claims challenged**
Kazakov and Bianchi	§ 103	3, 12, 13, 15, and 18
Kazakov and Mutter	§ 103	3, 12, 13, 15, and 18
Lo 1997	§ 102(a)	3, 12, 13, 15, and 18
Lo 1997, Lo 1990, and Lo 1989	§ 103	3, 12, 13, 15, and 18
Simpson, Schallhammer, Kazakov, and Bianchi	§ 103	3, 12, 13, 15, and 18
Simpson, Schallhammer, Kazakov, and Mutter	§ 103	3, 12, 13, 15, and 18
Kazakov	§ 102(b)	8

II. ANALYSIS

A. Effective Filing Date

As discussed in the decision to institute in IPR2012-00022, Lo 1997 (Ex. 1016) and Schallhammer (Ex. 1043) only qualify as prior art if the '540 patent is not entitled to priority under 35 U.S.C. §§ 119 and 120 to British priority application serial number 9704444, filed March 4, 1997. *See* IPR2012-00022, Paper 24 at 9. For the reasons set forth in that decision (*see id.* at 9-13), we accord the '540 patent an effective filing date of March 4, 1998, that is, the filing date of the PCT application resulting in the '540 patent.

We have considered Isis' arguments that it is entitled to the filing date of the GB priority application (Prelim. Res. 7-16), but do not find them convincing for the reasons set forth in the decision to institute in IPR2012-00022. In particular,

while Isis relies on WO 91/08304 (Ex. 2061) as demonstrating that the sex of a fetus was determined at 6 weeks using cytogenic analysis of chorionic villus culture (Prelim. Res. 15), that does not respond to the finding that the 12-40 week time period in the British priority application and the 7-40 week time period in the '540 patent represented a difference in the ability of the disclosed method to detect the DNA of fetal origin. *See* IPR2012-00022, Paper 24 at 9-12. That is, the skilled artisan, reading the '540 patent, would understand that the DNA of fetal origin that could be detected using the disclosed methods could be from a fetus from 7 to 40 weeks of gestation. The skilled artisan, however, upon reading the British priority application, would understand that the DNA of fetal origin that could be detected using the disclosed methods could be from a fetus from 12 to 40 weeks of gestation. *Id.* at 12.

B. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Technology, Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We interpret the claim terms in the independent claims as discussed in IPR2012-00022 (Paper 24 at 4-9). Isis presents additional argument as to why the Board was incorrect in its construction of those terms, such as the term "detecting" (Prelim. Res. 1-7), but we decline to revisit the interpretation of such claim terms in this decision.

Petitioner Ariosa presents what it believes to be the broadest reasonable interpretation of claim terms found in the dependent claims, such as the term "concentration" found in claim 13 (Pet. 19-23). As Isis does not address specifically the claim interpretation proffered by Ariosa as to the dependent claims challenged in the instant proceeding, and does not make any arguments specific to the dependent claims in response to Ariosa's challenges, we decline to address that proffered interpretation at this time.

C. Anticipation by Kazakov (Ex. 1014).

Claim 8 is drawn to the method of claim 1, with the added limitation "wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected." Ariosa notes that the Board determined that it had failed to establish a reasonable likelihood that claim 8 was anticipated by Kazakov in IPR2012-00022 (Pet 54, citing IPR2012-00022, Paper 24 at 26). Specifically, the decision to institute determined that Ariosa had failed to demonstrate what was amplified by the B1 and C2 primers described by Kazakov (*id.*).

As discussed in the decision to institute inIPR2012-00022 (Paper 24 at 19-20), Kazakov teaches that it is known that extracellular DNA is contained in the blood of humans and animals (Kazakov (Ex. 1014) at 232). Kazakov studied the sera from blood of women in both the first and third trimesters of pregnancy, as well as women with late toxicosis of pregnancy (*id.* at 233). Kazakov then performed PCR using DNA preparations from the serum using primers for Alu repeats (*id.*). The primers used by Kazakov were the Tc65, B1, and C2 primers (*id.*).

Kazakov reported that during pregnancy, there is initially an increase in concentration of low-molecular weight DNA, and that inter-ALU repeats have

been detected only in the blood of women in the first trimester of pregnancy (*id.* at 234). Kazakov notes that both the cells of the fetus (trophoblasts) and the mother (cells of the endometrium and lymphocytes) may excrete DNA (*id.* at 235).

Ariosa cites a second declaration[2] of Dr. Mansfield[3] ("second Mansfield Declaration," Ex. 1047) to support the proposition the samples from pregnant women would inherently contain fetal DNA, and that sequences from the Y chromosome could be amplified and detected using PCR (Pet. 54, citing Ex. 1047 at ¶ 69). Ariosa also cites a second declaration[4] of Prof. Kazakov (Ex. 1046) as demonstrating that the B1 and C2 primers "would have resulted in an amplification product from non-Y chromosomes" (*id.* at 54, citing Ex. 1046 at ¶¶ 81-82).

Prof. Kazakov states that as demonstrated by an *in silico* database search,[5] the B1 and C2 primers would have amplified regions on multiple non-Y chromosomes (Ex. 1046 at 40, ¶ 81). Prof. Kazakov testifies further that the Alu repeats that would have been amplified using the B1 and C2 primers are fairly uniform in size, and thus would be visualized on a polyacrylamide gel as a single band (*id.*).

Isis asserts that Ariosa's challenge of claim 8 relies on an overly broad claim interpretation, as Kazakov does not distinguish paternally inherited DNA from maternally inherited (Prelim. Res. 17).

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[2] The first declaration of Dr. Mansfield was submitted in IPR2012-00022 (Ex. 1047).

[3] Dr. Mansfield has over thirty years of experience in genetic testing, including prenatal testing (Ex. 1047 at 1, ¶ 2; *see also id.* at 1-16, ¶¶ 2-12). Dr. Mansfield thus appears to have the requisite familiarity with molecular genetic testing that would be expected by one of skill in the art, and we credit her testimony.

[4] The first declaration of Prof. Kazakov was submitted in IPR2012-00022 (Ex. 1046).

[5] *See* Exhibits 55 and 56 of the Kazakov Declaration.

As set forth in the claim construction analysis set forth in IPR2012-00022 (Paper 24 at 4-9), the detection step of claim 1, on which claim 8 depends, does not require distinguishing nucleic acid as being inherited from the father or even as being from the fetus, only that it be identified as containing some level of nucleic acid. The Kazakov reference meets that limitation, as it identifies the amplified nucleic acid from the serum of pregnant females (*see* Kazakov, Inset VIII, Figures 1 and 2).

Isis further argues that even with the erroneous claim construction, Kazakov fails to meet the limitations of claim 8. Isis contends that Kazakov only amplified a single Alu fragment using the B1/C2 primers, whereas Ariosa allegedly provides evidence that Kazakov amplified multiple chromosomes, including the Y chromosome, using those primers (Prelim. Res. at 17-18). Because Kazakov produced only a single product, Isis asserts that the reference "cannot have *necessarily* amplified the Alu sequences on each and every chromosome alleged by Ariosa to have been amplified" (*id.* at 18).

As testified by Prof. Kazakov, the Alu repeats that would have been amplified using the B1 and C2 primers are fairly uniform in size, and thus would be visualized on a polyacrylamide gel as a single band (Ex. 1046 at 40, ¶ 81). Prof. Kazakov is the author of the Kazakov reference (Ex. 1046 at 1, ¶ 1), has a graduate degree and has done research and taught in the biological sciences (*id.* at 1-3, ¶¶ 2-4). Prof. Kazakov also has multiple publications in the field of cytology and molecular biology (*id.* at 3-6, ¶¶ 5-6). Prof. Kazakov thus appears to have the requisite familiarity with molecular biology that would be expected by one of skill in the art, and we credit his testimony.

Isis contends further that, "even if serum inherently contains fetal cell free DNA," it does not necessarily follow that Kazakov "inherently *amplified* or

detected it because maternal nucleic acid *alone* may have been detected" (Prelim. Res. 19). According to Isis, Kazakov did not detect any amplification product using the Tc65 primer to amplify the serum of women with preeclampsia, but that fetal cell free DNA is in fact raised 86-fold during preeclampsia (*id.*). Thus, Isis asserts, if Kazakov "had necessarily amplified *fetal* cell free DNA, the pre-eclampsia samples would have been positive for Tc65 amplification" (*id.*). As they were not, Isis contends that Kazakov did not amplify cell free DNA (*id.*).

As noted in IPR2012-00022 (Paper 24 at 24), the fact that Kazakov observed amplification of nucleic acid in the first trimester and not the third trimester does not necessarily demonstrate that extracellular DNA from the fetus was absent in the serum to be amplified. In fact, it would be against the weight of evidence of record, as both Petitioner and Patent Owner appear to agree, that the presence of extracellular nucleic acid from the fetus in the serum or plasma of the pregnant female is an inherent property of that serum or plasma. Accordingly, the alleged inconsistency in Kazakov is insufficient on this record to convince us that Kazakov did not inherently amplify fetal DNA.

Isis argues further that as Ariosa's petition "submits the same prior art (Kazakov) *and* makes substantially the same argument (inherent anticipation)," the Board should exercise its discretion under 35 U.S.C. § 325(d) and deny Ariosa's petition as to claim 8 (Prelim. Res. 47).

In IPR2012-00022, we denied institution as to claim 8 as being anticipated by Kazakov on the basis that it was unclear what was amplified by the B1 and C2 primers described in the Kazakov reference, as Ariosa did not point to where Exhibits 48-49 referenced in footnote 30 of Professor Kazakov's Declaration could be found (IPR2012-00022, Paper 24 at 25). Ariosa thus has corrected what

appears to be an oversight, and we thus decline to exercise our discretion not to institute *inter partes* review of claim 8 as being anticipated by Kazakov.

We, therefore, conclude that Ariosa has demonstrated a reasonable likelihood that it will prevail in its challenge that claim 8 is anticipated by Kazakov.

D. Anticipation by Lo 1997 (Ex.1016).

Ariosa notes that in IPR2012-00022, the Board determined that Ariosa had established a reasonable likelihood that independent claim 1, as well as dependent claims 2 and 5, are anticipated by Lo 1997 (Pet. 33). Ariosa contends that claims 3, 12, 13, 15, and 18 are anticipated also by Lo 1997 (*id.* at 33-37).

Lo 1997 studied whether fetal DNA could be detected in maternal plasma and serum (Lo 1997 (Ex. 1016), p. 485, second col.). Blood samples were collected from pregnant women, and the plasma and serum were obtained (*id.*). The DNA was extracted and processed for PCR (*id.*). Primers for Y chromosome specific sequences were used, and it was determined that from the 43 women from whom plasma and serum were collected, there were 30 male and 13 female fetuses (*id.* at 486, first col.). Lo 1997 thus noted that the "results show that fetal DNA is present in maternal plasma and serum," and that "[u]se of maternal plasma or serum for the detection of fetal DNA for non-invasive prenatal diagnosis may therefore be possible" (*id.*).

Claims 3, 12, 13, 15, and 18 each ultimately depend from independent claim 1, which claim the Board already has determined to be subject to challenge in a trial before the Board based on Ariosa's demonstration that there is reasonable likelihood that claim 1 is anticipated by Lo 1997. Isis has not submitted any further argument as to Ariosa's position that dependent claims 3, 12, 13, 15, and 18

are also anticipated by Lo 1997, and we thus conclude that Ariosa has demonstrated a reasonable likelihood that those claims are anticipated also by Lo 1997.

E. Obviousness of claims 3, 12, 13, 15, and 18 over Kazakov and Bianchi or Simpson, Schallhammer, Kazakov, and Bianchi

Ariosa notes that the Board determined in IPR2012-00022 that Ariosa had established a reasonable likelihood that independent claim 1, as well as dependent claims 2 and 5, are anticipated by Kazakov. In addition, the Board had determined also that the claims were rendered obvious by the combination of Simpson, Schallhammer, and Kazakov (Pet. 43).

Ariosa relies on Bianchi to meet the limitation of the dependent claims (Pet. 24-28; *see also id.* at 43-48). Ariosa points to where in Bianchi those additional limitations may be found, and how they remedy any deficiencies of either Kazakov or the combination of Simpson, Schallhammer, Kazakov, and Bianchi (*see id.*). Ariosa also relies on the Declarations of Dr. Mansfield (Ex. 1047) and Dr. Kazakov (Ex. 1046) to establish why the ordinary artisan would have combined the teachings of Bianchi in the method of Kazakov (Pet. 26-28; *see also id.* at 45-48).

Isis argues that Ariosa has failed to establish a *prima facie* case of obviousness as there was no reasonable expectation of detecting fetal nucleic acid in serum or plasma successfully (Prelim. Res. 20; *see also id.* at 41). In particular, Isis argues that the presence of fetal cells in maternal blood was rare (*id.* at 26-27).

Isis further contends that the art taught away from using serum or plasma to detect fetal nucleic acid (Prelim. Res. 20). Specifically, according to Isis, before the filing of the ’540 patent, significant effort was used to try and isolate fetal cells

from maternal blood in order to develop non-invasive detection methods for fetal nucleic acid; and that serum and plasma were in fact discarded (*id.* at 25, citing Ex. 2048 at 518 and Ex. 2071 at 763).

The arguments presented by Isis go to the patentability of independent claim 1, and were addressed in IPR2012-00022 (paper 24 at 30-31). As Isis does not address specifically the limitations added by dependent claims 3, 12, 13, 15, and 18, we conclude that Ariosa has demonstrated a reasonable likelihood that those claims are rendered obvious by the combination of Kazakov and Bianchi or the combination of Simpson, Schallhammer, Kazakov, and Bianchi.

Secondary Considerations

Isis asserts in response to the obviousness rejections that Isis has significant objective evidence of nonobviousness (Prelim. Res. 28). Note, that as Isis does not argue secondary considerations particularly as to any of the claims challenged in the instant proceeding, we will not attempt to ascertain on this record which arguments as to secondary considerations correspond to which claims. Moreover, Isis has failed to show that the evidence of secondary considerations arises from the claimed and novel features. *See, e.g., Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

Other Challenges

As to the other challenges asserted by Ariosa, those asserted grounds are unnecessary in light of the determination that there is a reasonable likelihood that all of the challenged claims are unpatentable on the challenges as set forth above. Accordingly, we decline to institute *inter partes* review of the challenged claims based on grounds other than those set forth above.

III. Order

It is therefore:

ORDERED that pursuant to 35 U.S.C. § 314 that *inter partes* review is hereby instituted for the following grounds:

I. Claim 8 under 35 U.S.C. § 102(b) as being anticipated by Kazakov;

II. Claims 3, 12, 13, 15, and 18 under 35 U.S.C. § 102(a) as anticipated by Lo 1997;

III. Claims 3, 12, 13, 15, and 18 are rendered obvious under 35 U.S.C. § 103(a) by the combination of Kazakov and Bianchi; and

IV. Claims 3, 12, 13, 15, and 18 are rendered obvious under 35 U.S.C. § 103(a) by the combination of Simpson, Schallhammer, Kazakov, and Bianchi.

FURTHER ORDERD that no other ground is authorized for *inter partes* review;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial commencing on the entry date of this decision;

FURTHER ORDERED that the parties Joint Proposed Schedule (IPR2012-00022, Paper 37) is adopted and Due Dates 1-7 are set accordingly; and

FURTHER ORDERED that because an initial conference call was already held in IPR2012-00022 on April 16, 2003, which is joined with this proceeding in the accompanying decision granting Ariosa's motion to join the two proceedings, an initial conference call in the current proceeding is not necessary. If the parties feel an additional initial conference call with the Board is necessary, they should contact the Board to arrange such a call.

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