United States District Court,
D. Connecticut.

APPLERA CORP,
Plaintiff.
v.
STRATAGENE CORP,
Defendant.

No. 3:04-CV-1881 (RNC)

March 12, 2007.

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MEMORANDUM OPINION ON CLAIM CONSTRUCTION

ROBERT N. CHATIGNY**, United States District Judge.**

This is a patent infringement case. Applera Corp. holds the right to U.S. Patent No. 6,814,934 ("the "4 patent"), which claims an instrument for monitoring the progress of a nucleic acid amplification reaction. Applera alleges that the patent is being infringed by defendant Stratagene Corp. Pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), the parties have asked the court to construe certain terms in the patent. I previously issued an oral ruling on the claim construction issues presented by the parties. This memorandum is intended to flesh out the basis for the prior ruling without altering the ruling insofar as the substance of the claim construction itself is concerned.

I. *BACKGROUND*

To study DNA, it is often necessary to amplify the DNA. The best known amplification method is the polymerase chain reaction (PCR). In PCR, DNA is amplified by repeatedly heating and cooling the DNA together with other chemicals. Each heating and cooling cycle entails three steps. First, the DNA is heated to a temperature at which the double-stranded segment separates (the "denaturing" phase). Then, in the "annealing" phase, the temperature is reduced so that a primer binds to the single strands. Finally, in the extension phase, a polymerase enzyme extends the primers to complete a double-stranded segment from each single strand. This cycle is repeated 30 to 40 times.

The "4 patent claims an instrument for monitoring an amplification reaction such as PCR. Fluorescent dyes

are added to the reaction mixture. As the reaction progresses, light is focused on the reaction vessels, and the fluorescent dyes glow brighter. An optical detector measures the amount of glow. Using this instrument, a scientist can track the progress of the reaction as it is taking place and quantify the starting amount of DNA.

The parent application for the "4 patent was filed in 1991, claiming methods for monitoring DNA amplification. The claims were rejected as obvious, even after several amendments. In 1997, the applicant filed a continuation application for an instrument for practicing the methods claimed in the first application. This application was also rejected as anticipated and obvious. After the applicant filed for reconsideration, the PTO again rejected the claims as obvious over Haff in view of Mackey, referring to an article published by Haff.

In 2000, the applicant filed amended claims and explained how they were distinguishable from Haff. These too were rejected several times.

In 2002, the Examiner granted the applicant a personal interview. At the interview, it was agreed (in the words of the Examiner) that "structural language requiring operation of the detector over the course of a thermal cycling amplification reaction would define over art of record." Amended claims were filed in 2002. The patent issued on November 4, 2004.

Within a week after the patent issued, Applera brought this suit. Named as defendants were Bio-Rad Labs, Inc., MJ Research, Inc., and Stratagene Corp. Bio-Rad Labs and MJ Research settled with Applera in February 2006, leaving Strategene as the lone defendant.

A *Markman* hearing was held on April 6, 2006. The court shared its tentative conclusions with the parties at the hearing and gave them the opportunity to submit supplemental briefs. An oral ruling setting forth the court's claim construction was provided to the parties during a telephone conference on May 5, 2006.

II. ***Basic Principles of Claim Construction***

Claim construction is governed by the methodology set forth by the Federal Circuit in Phillips v. AWH Corp., 415 F.3d 1303 (Fed .Cir.2005) (en banc), *cert. denied,* 164 L.Ed.2d 49 (2006). The process begins with the words of the claim itself. Id. at 1312-13. Claims should be given their ordinary and customary meaning, as understood by "a person of ordinary skill in the art in question at the time of the invention." Id. at 1313.

The claim must be read in light of the specification. Id. at 1315. The specification is "the single best guide to the meaning of a disputed term." *Id*. (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996)). The specification may contain a specific definition for a term that differs from its ordinary meaning. Id. at 1316. Similarly, the specification may reveal an intentional disclaimer of claim scope by the inventor. *Id*.

In consulting the specification, a court must be careful to use the specification to interpret the claim, not limit it. *Id*. at 1323; *see also* Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1117 (Fed.Cir.2004). For example, although the specification may describe specific embodiments, the claim should not necessarily be confined to those embodiments. Phillips, 415 F.3d at 1323. Conversely, the claim should not be interpreted in a way that would exclude a preferred embodiment described in the specification.

Cytologix Corp. v. Ventana Med. Sys., Inc., 424 F.3d 1168, 1175 (Fed.Cir.2005).

The court should also consult the prosecution history, which provides evidence of how the inventor understood the invention. Phillips, 415 F.3d at 1317. The prosecution history is apt to be less useful than the specification because it is often ambiguous. *See id*. For this reason, the Federal Circuit requires that disavowals of claim scope in the prosecution history be clear and unmistakable. Sorensen v. Int'l Trade Comm'n, 427 F.3d 1375, 1378-79 (Fed.Cir.2005). Moreover, the court should focus on the statements of the applicant, not the examiner. Id. at 1379. If the prosecution history does not contain a clear disclaimer of claim scope, it may still provide some assistance to the court in choosing between competing definitions of claim terms. *See* Novartis Pharm. Corp. v. Eon Labs Mfg., Inc., 363 F.3d 1306, 1311 (Fed.Cir.2004).

Finally, the court may consult extrinsic evidence, such as expert and inventor testimony, dictionaries, and learned treatises. Phillips, 415 F.3d at 1317. Extrinsic evidence is especially useful when the intrinsic evidence is insufficient to enable the court to construe the claims. Vitronics Corp., 90 F.3d at 1584. However, extrinsic evidence is less reliable than intrinsic evidence, and the court should discount any expert evidence that is at odds with the intrinsic evidence. Phillips, 415 F.3d at 1318 . FN1

FN1. In *Phillips,* the Federal Circuit cautioned against overreliance on dictionaries, observing that using dictionaries to construe claims "focuses the inquiry on the abstract meaning of words rather than on the meaning of claim terms within the context of the patent." *Id*. at 1320-21. Nonetheless, dictionaries can be useful in understanding commonly used words. *See* Free Motion Fitness, Inc. v. Cybex Int'l, Inc., 423 F.3d 1343, 1348 (Fed.Cir.2005).

III. *THE CLAIM TERMS AT ISSUE*

The "4 patent claims:

1. An instrument for use in monitoring a nucleic acid amplification reaction comprising multiple thermal cycles, comprising:

(a) an automated thermal cycler capable of alternately heating and cooling, and adapted to receive, at least one reaction vessel containing an amplification reaction mixture comprising a target nucleic acid, reagents for nucleic acid amplification, and a detectable nucleic acid binding agent; and

(b) a detector operable to detect a fluorescence optical signal while the amplification reaction is in progress and without opening the at least one reaction vessel, which fluorescence optical signal is related to the amount of amplified nucleic acid in the reaction vessel. FN2

FN2. Similar language also appears in claim 7, a system claim. The disputed terms are identical in both claims.

The parties have asked the court to focus on the following terms:

A. "while the amplification reaction is in progress"

Applera asks the court to construe this language to mean "during the amplification reaction," which would

include either periodic or constant monitoring. Stratagene argues that the term should be construed to mean "for so long as the amplification reaction is taking place," which would require that the instrument be operable to conduct constant monitoring, even if the user wanted to monitor fluorescence only periodically. In the alternative, in its post-hearing brief, Stratagene asks the court to interpret the term to require that the instrument be operable to conduct intra-cycle monitoring.

The claim language itself provides insufficient guidance for resolving the parties' dispute. Both parties' interpretations are consistent with the plain meaning of the words. Accordingly, I consult the specification, which is "the single best guide to the meaning of a disputed term." Phillips, 415 F.3d at 1315 (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996)).

The specification does not exclude either parties' interpretation, although Applera's flows more naturally from the specification. As Stratagene notes, the specification contains references to constant monitoring. For example, it teaches that "the continuous detection of fluorescence throughout the amplification provides an amplification profile that reflects the amount of target present at start." (Col.24, lns.9-12.) However, as Applera observes, there are also references to periodic monitoring. For instance, the specification teaches, "It is appropriate to 'read' the microtiter plate before and after thermocycling for determining fluorescence." (Col.12, lns.36-39.) Similarly, it states, "[B]ecause fluorescence can be determined between cycles during the course of a PCR.... [M]onitoring fluorescence while PCR is in progress serves to quantitate small amounts of DNA." (Col.16, lns.22-24, 29-32.) This latter quotation is particularly significant because it ties periodic detection to the phrase "while PCR is in progress."

Stratagene argues that the specification's references to continuous monitoring reflect the inventor's understanding that the instrument had to be operable to detect constantly, even if it was only used to conduct periodic monitoring. Although the specification does not exclude this reading, it certainly does not require it either. A more natural reading of the specification is that the inventor did not consider whether the detector had to be operable to conduct constant monitoring. Under this reading, the detector merely has to be operable to detect the fluorescence signal, whether constantly or periodically, so long as the detection occurs during the amplification reaction. This reading is preferable, particularly given the explicit reference to inter-cycle detection as occurring "while PCR is in progress."

Because the specification does not provide clear guidance, I turn to the prosecution history. The parties discussed the prosecution history at length during the *Markman* hearing. The discussion centered on the examiner's rejections of the patent as obvious in light of the Haff reference and the inventor's subsequent amendments to the claim.

I understand the Haff instrument to work as follows. Identical amounts of the same target DNA are placed in different reaction vessels. Identical reactions are run within each vessel. The reactions are stopped after various reaction cycles. After a reaction is stopped, the vessel is opened and dye is added. The fluorescence is measured and plotted on a graph. By this process, one can track the amplification reaction for that target piece of DNA. In first rejecting the invention as obvious in light of Haff, the examiner understood Haff to involve monitoring "during the thermal cycling process." (Bio-Rad Ex. 1, at 190.) The Examiner explained that it would be obvious to one trained in the art to optically couple the fluorescence detector to the thermal cycler to measure fluorescence without transferring samples from the cycler to the detector. (Bio-Rad Ex. 1, at 191.)

In response to the obviousness rejection, the inventor explained:

With applicant's invention, the amplification takes place and is detected in a sealed vessel condition. During amplification, a real-time signal indicative of a cycle-dependent change in double-stranded nucleic acid is generated to allow monitoring of the accumulation of double-stranded product while the amplification reaction is in progress, without opening the reaction vessel, without taking aliquots, and without withdrawing samples. Once the amplification reaction is initiated, no further handling or manipulative steps are required.

....

... Also, by generating a signal that not only gives an indication of the inter-cycle net change of double-stranded product but intra-cycle variations as well, applicant's claimed instrument eliminates any ambiguities regarding the time of sampling. The signal generated by applicant's claimed invention is independent of the time of sampling.

(Bio-Rad Ex. 1, at 204-05.) The Examiner nonetheless rejected the claims, finding these arguments "directed solely to the intended use of the apparatus, rather than the structural features thereof." (Bio-Rad Ex. 1, at 212.) He also stated that it would have been obvious to use sealed reaction vessels to prevent contamination. (Bio-Rad Ex. 1, at 212.)

In response, the inventor explained that "Haff et al. failed to recognize that an indicator reagent could be included in a nucleic acid reaction mixture to allow amplification to be measured over multiple cycles without opening the reaction vessel." (Bio-Rad Ex. 1, at 249.) The Examiner again rejected this explanation, citing other prior art (i.e., Schnipelsky) showing that detection reagents would not interfere with the reaction. (Bio-Rad Ex. 1, at 276.)

Following these communications, the Examiner and inventor had a personal interview. After the interview, the Examiner wrote, "It was generally agreed that *structural* language requiring operation of the detector over the course of a thermal cycling amplification reaction would define over the art of record." (BioRad Ex. 1, at 302.) Thereafter, the applicant filed an amended claim containing the language, "while the amplification reaction is in progress." He remarked, "During the interview, applicant's representatives summarized prior arguments. The Examiner agreed that the rejection over the art of record would be withdrawn if the claims more clearly recited that the detector was operable to detect during the amplification reaction, in contrast to a detector that was not operable during an amplification reaction." (Bio-Rad Ex. 1, at 317.)

After reviewing the prosecution history in detail, and focusing on the claimed apparatus, as Stratagene urges me to do, I find the prosecution history too ambiguous to support Stratagene's narrower construction.

The claimed invention is distinguishable from Haff in that the dye is present in the reaction mixture as amplification takes place and the fluorescence can be measured without opening the vessels to withdraw samples or to inject dye. As the inventor explained in 2000, one benefit of his invention is that it can generate a intra-cycle signal, whereas Haff's plainly cannot. Until 2002, the Examiner consistently rejected these differences between Haff and the invention and held the claimed invention obvious in light of Haff and other references.

We do not know exactly what happened in the 2002 interview. According to Stratagene, the Examiner

concluded that a key distinction between the claimed invention and Haff was that Haff could constantly detect fluorescence "over the course of a thermal cycling amplification reaction." On this view, "while the amplification reaction is in progress" must be construed to embody the inventor's and the Examiner's understanding that the claimed invention was structurally operable to detect constantly throughout the entire reaction or, in the alternative, within cycles as opposed to only between cycles.

However, Applera's version of what happened at that meeting is equally, if not more, plausible. According to Applera, the personal interview persuaded the Examiner that Haff did not teach detection "during" the amplification reaction, as he had earlier thought. Accordingly, he agreed to withdraw the objections if it was made clearer that the claimed instrument was operable to detect fluorescence during the reaction. This interpretation is supported by the inventor's statement that his representatives summarized prior arguments. Importantly, he did not state that they presented new arguments or distinguished his invention on the ground that it was operable to constantly monitor fluorescence. On the basis of the prior arguments, the Examiner agreed to withdraw the objections in exchange for clearer structural language requiring that the detector be operable to detect during the reaction.

The prosecution history is simply too ambiguous to support the narrower construction proposed by Stratagene. This ambiguity manifests itself in the varying language used by the Examiner and the inventor. In his record of the interview, the Examiner used the language "over the course of the thermal cycling amplification reaction." However, the inventor summarized that same conversation using the word "during." Moreover, in a later document, the Examiner contrasted the invention, which would detect "throughout" the amplification reaction, with an instrument that limited "detection to a time immediately following the amplification reaction." (Bio-Rad Ex. 1, at 438.) This suggests that the Examiner understood "throughout" to mean something like "during."

This analysis reconfirms what I said during the *Markman* hearing. This is an imperfect process. The fact that we have to speculate about what the Examiner and the inventor had in mind underscores the ambiguity of the prosecution history. Given these ambiguities, and given that Stratagene's narrow construction is not compelled by the intrinsic evidence, I find it appropriate to focus on the plaintiff's statements in deciding whether he limited his claim in the way urged by Stratagene. I cannot conclude that he did.

For these same reasons, I reject Stratagene's alternative argument that the detector must be operable to detect within cycles. The inventor did describe his invention as "generating a signal that not only gives an indication of the inter-cycle net change of double-stranded product but intra-cycle variations as well." (Bio-Rad Ex. 1, at 204-05.) But he characterized this as an "advantage" of his system, not as a "structural and functional difference[ ]." (Bio-Rad Ex. 1, at 204.) This advantage derives from the structural difference that, in the claimed invention, the detectable nucleic acid binding agent is present in the reaction vessel as the reaction takes place. A detector operable to detect intra-cycle variations could be used to take advantage of this structural difference. But this statement does not necessarily mean that the detector must be operable to detect intra-cycle variations, particularly in light of the specification's references to inter-cycle monitoring.

The limited scope sought by Stratagene is not required by the intrinsic evidence. Accordingly, I construe "while the amplification reaction is in progress" to mean "during the amplification reaction."

B. "automated thermal cycler"

Applera asks the court to construe this term as "an instrument for use in a nucleic acid amplification

reaction comprising multiple thermal cycles for alternately heating and cooling samples." Stratagene advocates defining the term as "an instrument that can be programmed to heat and cool a surface or vessel." I adopt Applera's definition.

To define "automated thermal cycler," I must determine how a person trained in the art would have understood the term in 1991. In doing so, I "must define the term in a manner consistent with the scientific and technical context in which it is used in the patent." *See* AFG Indus., Inc. v. Cardinal IG Co., 239 F.3d 1239, 1248 (Fed.Cir.2001).

Although the specification does not define "automated thermal cycler," it uses the term in a way consistent with Applera's proposed construction. Every reference to "thermal cycler" or "thermocycler" appears to identify an instrument used for conducting nucleic acid amplification reactions comprising multiple thermal cycles.

At the *Markman* hearing, Applera presented the testimony of Dr. Carl Batt, who testified that persons trained in the art in 1991 would have understood "automated thermal cycler" as a specialized instrument for use in a nucleic acid amplification reaction comprising multiple thermal cycles for alternately heating or cooling samples. I credit his testimony. Based on the fact that he authored a paper describing PCR technology submitted for publication in 1991 (*see* Tr. 74-76), I find that he was trained in the art in 1991 and is qualified to testify on this issue. Stratagene has presented no evidence suggesting that persons trained in the art of nucleic acid amplification in 1991 would have understood this term in any other way.

I acknowledge the Federal Circuit's admonition that extrinsic evidence is less reliable than intrinsic evidence. Phillips, 415 F.3d at 1318. In *Phillips,* the Federal Circuit advised courts to discount expert evidence at odds with the intrinsic evidence. *Id*. Nonetheless, consulting extrinsic evidence is appropriate when the internal evidence is ambiguous. *See* Storage Tech. Corp. v. Cisco Sys., Inc., 329 F.3d 823, 832 (Fed.Cir.2003). Dr. Batt's testimony does not contradict the internal evidence; to the contrary, it is consistent with the specification's use of the term.

Stratagene's proposed construction is too broad and does not reflect the scientific and technical context of the patent. Stratagene's only support for its proposed construction is the specification's reference to "a spectrafluorometer capable of heating and cooling a surface, or vessel." (Col.12, lns.14-15.) The specification contrasts this to a spectrafluorometer housed independently of a thermocycler. As Stratagene itself notes in its post-hearing brief, the specification was first drafted for the method patent application. For this reason, the specification reads more broadly than the claim itself. For example, as discussed below, the specification refers to various methods of DNA amplification, including isothermal reactions. But the claimed instrument is limited to reactions comprising multiple thermal cycles. Likewise, the specification refers to various methods of detecting nucleic acid amplification, even if the claimed instrument performs only one such method. My conclusion that the amplification reaction must comprise multiple thermal cycles reinforces the proper construction of "thermal cycler." The evidence shows that a person trained in the art in 1991 would have understood "thermal cycler" or "thermocycler" in the context of amplification reactions comprising multiple thermal cycles in the way suggested by Dr. Batt.

After reviewing the claim language, the specification, and the extrinsic evidence (i.e., Dr. Batt's testimony), the only conclusion consistent with the context of this patent is that "thermal cycler" refers to "an instrument for use in a nucleic acid amplification reaction comprising multiple thermal cycles for alternately heating or cooling samples."

C. "amplification reaction"

Based on the presentations at the *Markman* hearing, the parties appear to agree that an "amplification reaction" is "any in vitro means for multiplying the copies of a target sequence of nucleic acid." The sole dispute is whether the reaction must comprise multiple thermal cycles, as suggested by the claim preamble.

A preamble limits the invention "if it is 'necessary to give life, meaning, and vitality' to the claim." Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed.Cir.2002) (quoting Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed.Cir.1999)). The court may construe the preamble as part of the invention if it "helps to determine the scope of the patent claim." NTP, Inc. v. Research in Motion, Ltd ., 418 F.3d 1282, 1305 (Fed.Cir.2005), *cert. denied,* 126 S.Ct. 1174 (2006). Similarly, the preamble should be construed as part of the invention when it provides antecedent basis for terms in the claim body. Id. at 1306.

Applera argues that the inventor intended the preamble to limit the scope of the claim to reactions "comprising multiple thermal cycles." Stratagene contends that the preamble merely recites a purpose of the invention. I agree with Applera. The claim refers to " *the* amplification reaction." As the Federal Circuit explained in *NTP, Inc.,* when a term is preceded by "the"-a word of limitation-it is appropriate to look back to the preamble as the antecedent basis for that term. *Id.* at 1306. In this case, looking back to the preamble reveals that "the amplification reaction" referenced in the claim is "an amplification reaction comprising multiple thermal cycles."

Moreover, the preamble breathes meaning into the claim because it provides context for the term "automated thermal cycler." The combined use of "thermal cycler" and "comprising multiple thermal cycles" demonstrates that the inventor intended to limit the instrument to one involving nucleic acid amplification occurring over multiple thermal cycles. Although the specification does mention other types of amplification reactions that do not comprise multiple thermal cycles, the claim language, as construed in light of the preamble, speaks for itself. *See* Phillips, 415 F.3d at 1312-13.

D. "nucleic acid binding agent"

In their claim construction briefs, Applera argued that it was unnecessary to construe this term, whereas Stratagene defined it as "a fluorescent dye or other chromophore, enzyme, or agent capable of producing a signal, directly or indirectly, when bound to double-stranded DNA, that is distinguishable from the signal produced when that same agent is in solution or bound to a single stranded nucleic acid."

Applera persuasively argues that Stratagene's proposed construction is too narrow because it limits the term to specific examples mentioned in the specification. Elsewhere in the specification, the inventor states that "any DNA binding agent is suitable." (Col.6, ln.60.) I therefore reject Stratagene's proposed construction as unduly narrow.

Although the specification provides that any DNA binding agent is suitable, it goes on to state, "so long as in the presence of that agent a net increase in the amount of double-stranded DNA present is reflected in a change [in] signal intensity that is detectable directly or indirectly." (Col.6, lns.60-64.) Therefore, it is appropriate to construe the disputed term as "any DNA binding agent so long as in the presence of that agent a net increase in the amount of double-stranded DNA present is reflected in a change in signal intensity that is detectable directly or indirectly."

E. "detector operable to detect a fluorescence optical signal"

In its claim construction brief, Stratagene urged the court to construe "operable" as meaning "capable of being used." However, the claim is perfectly clear on its face, and there is no significant disagreement between the parties as to its meaning. Stratagene has done little to argue that this term needs to be construed, and it does not press this point in its post-hearing brief. Therefore, it is unnecessary to construe this term.

F. "without opening the at least one reaction vessel"

Although the parties addressed this term in their briefs, they agree that it does not require construction.

III. *Conclusion*

To summarize, I have construed the disputed terms as follows:

A. "while the amplification reaction is in progress"-during the amplification reaction;

B. "automated thermal cycler"-an instrument for use in a nucleic acid amplification reaction comprising multiple thermal cycles for alternately heating or cooling samples;

C. "amplification reaction"-any in vitro means for multiplying the copies of a target sequence of nucleic acid comprising multiple thermal cycles;

D. "nucleic acid binding agent"-any DNA binding agent so long as in the presence of that agent a net increase in the amount of double-stranded DNA present is reflected in a change in signal intensity that is detectable directly or indirectly;

E. "detector operable to detect a fluorescence optical signal"-no need to construe;

F. "without opening the at least one reaction vessel"-no need to construe.

D.Conn.,2007.
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