UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THERMO FISHER SCIENTIFIC INC.
Petitioner

v.

Bio-Rad Laboratories, Inc.
Patent Owner

Patent No. 8,236,504
Issued: August 7, 2012
Filed: June 30, 2010
Inventors: Kordunsky *et al*.

Title: SYSTEMS AND METHODS FOR FLUORESCENCE DETECTION WITH A MOVABLE DETECTION MODULE

Inter Partes Review No. – IPR2017-00055

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,236,504 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123

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I. Statement of the precise relief requested and the reasons therefor (37 C.F.R. § 42.22(A))

Thermo Fisher Scientific Inc. petitions for *Inter Partes* Review, seeking cancellation of claims 1-3, 6-11, 13-17 and 19-22 of U.S. Patent No 8,236,504 to Kordunsky *et al*. ("the '504 Patent," Ex. 1001), which on its face indicates that the assignee is Bio-Rad Laboratories, Inc. (no assignment recorded for this patent). As detailed below, claims 1-3, 6-11, 13-17 and 19-22 are unpatentable for obviousness.

II. The '504 Patent disclosure and claims

The '504 Patent, titled "Systems And Methods For Fluorescence Detection With A Movable Detection Module," issued on Aug. 7, 2012, from U.S. App. No. 12/827,521, filed on Jun. 30, 2010. Ex. 1001. The '504 Patent claims priority to App. No. 11/555,642 filed Nov. 1, 2006, which is a continuation of App. No. 10/431,708, filed May 8, 2003. *Id*.

The '504 Patent claims. The '504 Patent has 22 claims, including independent claims 1 and 13. Exemplary claim 1 is provided below:

> 1. A fluorescence detection apparatus for analyzing samples located in a plurality of wells in a thermal cycler, the apparatus comprising:
>
> a support structure attachable to the thermal cycler;
>
> a shuttle movably mounted on the support structure; and
>
> a detection module attached to the shuttle, the detection module including:

a housing having an opening oriented toward the plurality of wells;

an excitation light generator disposed within the housing; and

an emission light detector disposed within the housing,

wherein, when the support structure is attached to the thermal cycler, a heating element is disposed between the detection module and the sample wells and the shuttle is movable to position the detection module in optical communication with different wells of the plurality of wells through a plurality of openings extending through the heating element.

Independent claim 13 is similar, but indicates among other things that the support is disposed within an exterior housing. Ex. 1001, claim 13.

III. Person of ordinary skill in the art

A person of ordinary skill in the art ("**artisan**") is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom, and has ordinary creativity. An artisan in the field of the '504 Patent (optical detection devices) would have known the literature concerning the design and manufacture of analytical instruments for biological applications, which included optical detection devices and scanning assemblies, such as thermal cyclers, sequencers, microarray readers, fluorimeters, plate readers and scanners before May 8, 2003. Ex. 1002, ¶13.

Regarding the claimed subject matter, an artisan would typically have had (i) an undergraduate degree (*e.g.*, B.Sc. or B.A.) in optics, physics, engineering (e.g., mechanical, electrical or structural), physical chemistry, chemistry, biology or the engineering, biological or chemical sciences, and have had at least about one year's experience in the design or manufacture of biological analytical instruments, *e.g.*, thermocyclers and scanners. Also, an artisan may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but of others on the team, *e.g.*, to solve a given problem. For example, a physicist, biologist, chemist and/or an optical engineer may have been part of a team. Ex. 1002, ¶14.

IV. Claim construction

No construction is needed, in accordance with 37 C.F.R. § 42.100(b), the terms are given their broadest reasonable interpretations (BRI) in view of the specification and file history. These interpretations are consistent with the claim constructions in Petitioner's concurrent petition IPR2017-00054 against the same claims on other grounds.

V. Identification of the challenge (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review of claims 1-3, 6-11, 13-17, 19-22 of the '504 Patent based on the unpatentability grounds summarized in the index below. Per 37 C.F.R. § 42.6(c), copies of the cited references accompany the Petition.

Ground	35 U.S.C. § (pre-3/16/2013)	Claims	Index of References
1	§103(a)	1-3, 6-11, 13-17, 19, 20, 22	Pantoliano, Miller and Gambini
2	§103(a)	21	Pantoliano, Miller, Gambini and Li

3	§103(a)	1-3, 6-8, 10, 13, 15-16, 19, 20, 22	Iwasaki, Pantoliano and Gambini
4	§103(a)	9, 11, 14 and 17	Iwasaki, Pantoliano, Gambini and Miller
5	§103(a)	21	Iwasaki, Pantoliano, Gambini and Li

U.S. Pat. 6,303,322 ("**Pantoliano**") published Oct. 16, 2001, and is prior art under pre-AIA §102(b). Pantoliano discloses a thermal cycler for PCR, and is better art than another patent also to Pantoliano applied during prosecution, which does not disclose a thermal cycler for PCR (U.S. Pat. 6,569,631). Ex. 1005, 42:57-62, Ex. 1027; Ex. 1002, ¶30. U.S. Pat. 5,528,050 ("**Miller**") published on Jun. 18, 1996, and is prior art under pre-AIA §102(b). WO 99/60381 ("**Gambini** ") published on Nov. 25, 1999, and is prior art under pre-AIA §102(b). Japanese Patent Pub. No. P2001-242081A ("**Iwasaki,**" certified translation provided) published on Sep. 7, 2001, and is prior art under pre-AIA §102(b). Chinese Patent Publ. No. CN1379236A ("**Li,**" certified translation provided) published in Chinese on Nov. 13, 2002, and is prior art under pre-AIA §102(a).

Each claim is challenged under two non-redundant Grounds, one based on Pantoliano as primary reference and the other on Iwasaki as primary. Pantoliano discloses a scanning cycler with a generator and detector placed outside the optics head; it would have obvious to place these in-head as a well-known alternative. In contrast, Iwasaki discloses a self-contained optics head with the generator/detector placed in-head; it would have been obvious to use such an optics head in thermal cyclers for scanning purposes. Thus, the Grounds are **not redundant**. The Grounds are also **not redundant** over other Grounds submitted in Petitioner's **concurrent petition** IPR2017-00054 against the same claims, since the Grounds herein are generally based on prior art under pre-AIA §102(b) under the asserted priority date, unlike the Grounds in the other petition. This Petition is supported by a declaration of Petitioner's expert, Professor Richard Mathies (Ex. 1002).

VI. Ground 1: Claims 1-3, 6-11, 13-17, 19, 20 and 22 would have been obvious in view of Pantoliano, Miller, and Gambini under pre-AIA §103(a)

As shown below, claims 1-3, 6-11, 13-17, 19, 20 and 22 would have been obvious over the combination of Pantoliano, Miller, and Gambini. The references together disclosed all elements of the claims, and there were many reasons to combine their teachings, making the claims obvious by their asserted priority date of 2003. A detailed *Graham* analysis is provided below for representative claim 1 and is also applicable to the other claims as well. *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

A) The first two *Graham* inquiries: Determining the scope and content of the prior art and ascertaining the differences from the claims: The scope and content of the art is such that there are no real differences between the challenged claims and the art; Pantoliano, Miller, and Gambini together disclose all elements of the claims, except for their combination together. Representative claim 1 is directed to a fluorescence detection apparatus in a thermal cycler ("**cycler**") which can monitor samples *in situ* in their wells, where a detection module ("**optics head**") is attached to a shuttle movably mounted on a support. The shuttle can move to place the optics head in view of different wells, for example by sequential scanning. Claim 1 has two more features: (1) the light generator and detector are placed within the optics head ("**in-head**") instead of outside it – a placement disclosed by Miller, and (2) a heating element with openings to allow scanning – already a standard component of cyclers, as acknowledged by the '504 Patent, and also taught by Gambini. It was obvious to include both these known features in Pantoliano's cycler by May 2003. Ex. 1002, ¶33.

Independent claim 1: As Professor Mathies explains, the combination of Pantoliano, Miller, and Gambini discloses all elements of claim 1.

Claim 1 (preamble). A person of ordinary skill in the art ("**artisan**") would have understood that all three references disclose a "*fluorescence detection apparatus for analyzing samples ... in ... wells*." Pantoliano combines two formerly-separate systems together into one single device: (1) thermal cycling block "for ... heating a plurality of samples" and (2) a real-time "fluorescent" sensor "for receiving spectral emission from the samples while ... heated," which "obviates the need to ... transfer the [heated] samples to another apparatus prior to taking" readings, resulting in "more accurate information" in real-time. Ex. 1005, 9:9-21, 9:47-58; Ex. 1002, ¶35. Pantoliano's device also has "a plurality of wells … for a plurality of samples." Ex. 1005, 33:37-40, Figs. 29-35; Ex. 1002, ¶35. Miller's apparatus is a "movable compact scan head" for "detection of ... fluorescence," for example in "microtiter" sample wells. Ex. 1006, 1:53-60, 3:2-5, 6:64-8, Figs. 1-4, 7; Ex. 1002, ¶35. Gambini's "monitoring instrument is mounted over ... [a] block containing ... vials" of samples. Ex. 1007, 6:30-31, Fig. 2; Ex. 1002, ¶35.

Pantoliano and Gambini both disclose that their apparatus are "*in a thermal cycler*" as further recited in claim 1 (preamble), and it was obvious that Miller's apparatus is suited for such use, as explained further below. Although applied to thermal-shift assays, Pantoliano's device is a thermal cycler that can "perform polymerase chain reaction, [or] thermal cycling steps for any purpose" as the "temperature of heat conducting block ... can be increased, decreased, or held constant." Ex. 1005, 42:57-62, 35:43-51; Ex. 1002, ¶36. Pantoliano uses a thermal cycler in some actual assays. Ex. 1005, 50:41-46; Ex. 1002, ¶36. Gambini's optical instrument is "mounted over" a block which is a "thermal cycler block." Ex. 1007, 6:30-31, 5:25-29; Ex. 1002, ¶36. Miller's optics head can act as a plate reader to scan "microtiter" wells – the most common sample wells in cyclers, such that some cyclers contained plate readers to scan wells, making Miller's optics head an obvious choice for cyclers. Ex. 1006, 1:13-15, 1:23-27, 3:2-5; Ex. 1010, 32; Ex. 1011, 178A, right col.; Ex. 1002, ¶36.

Claim 1(a). Artisans would have understood that all three references taught or suggested "*a support structure attachable to the thermal cycler*." For example, Pantoliano discloses a variety of internal structures such as a "relative movement means 3130", a "servo controller 3118" a "filter housing 3160" that are all interconnected, and are attached to the "base 3100" of the cycler, directly or indirectly. Ex. 1005, 35:7-36:2, Figs. 31-35; Ex. 1002, ¶37. As discussed for claim 1(b) below, these structures act as supports for a movable shuttle which is directly or indirectly mounted onto them. Ex. 1002, ¶37. Miller's optics head can be "moved ... along a rail" support which is attachable to any device of interest. Ex. 1006, 4:52-64; Ex. 1002, ¶37.

Claim 1(b). Artisans would have understood that Pantoliano and Miller disclosed, and Gambini suggested, a "*shuttle movably mounted on the support*." Pantoliano's system includes a shuttle in the form of a "sensor armature 3120" which is movably mounted on the various support structures discussed above, directly or indirectly (*e.g.*, elements 3118, 3160, 3130 or base 3100 of the cycler). Ex. 1005, 35:7-36:2, Figs. 31-35; Ex. 1002, ¶38. The '504 Patent affirms that the shuttle can be mounted indirectly on the support, for example through a "movable mounting" means. Ex. 1001, 5:44-6:4; Ex. 1002, ¶38. Pantoliano's shuttle is movably mounted on a support since it is connected to a "relative movement means 3130" that is in turn attached to Pantoliano's interconnected support structures discussed above. Ex. 1005, 35:7-36:2, Figs. 31-35; Ex. 1002, ¶38. Miller also discloses a movably-mounted shuttle in the form of a "support wall" attached to a "means for moving 76," where the components of the optics head are mounted on this shuttle. Ex. 1006, 5:52-58, 4:52-64, Fig. 4; Ex. 1002, ¶38.

Claim 1(c). Artisans would have understood that all three references disclosed a "*detection module*" ("**optics head**"), which is further "*attached to the shuttle*" in Pantoliano and Miller. Pantoliano discloses an optics head that is a "sensor" – such as a fiber-optic probe or a CCD camera – attached to a movable shuttle in the form of a "sensor armature." Ex. 1005, 35:19-35, 33:1-8, 40:39-41, Figs. 31-38; Ex. 1002, ¶39. In particular, a "sensor such as fiber optic probe 3122 or CCD camera 3000 is moved over … samples" where the "sensor is removably attached to a sensor armature" (shuttle), "so that the sensor is sequentially positioned over each sample." *Id*. Miller discloses an optics head that is a "movable compact scan head," which is mounted on a shuttle in the form of a "support wall" attached to a "means for moving." Ex. 1006, 1:53-54, 5:52-58, 4:52-64, Fig. 4; Ex. 1002, ¶39. Gambini similarly discloses an optics head such as a "scanning device ... with a single photodetector" that is "mounted over" the thermal cycling block, making a movable shuttle obvious. Ex. 1007, 11:15-16, 6:30-31; Ex. 1002, ¶39.

Claim 1(d). Artisans would have understood the detection modules ("**optics head**") of all three references each had a "*housing*." Miller's optics head is shown in Figs. 1-4 and 7 to have a box-like housing enclosing all optical components "within a small space." Ex. 1006, 1:55-56, Figs. 1-4, 7; Ex. 1002, ¶40. Pantoliano's optics head includes a "sensor such as fiber optic probe 3122 or CCD camera 3000 ... moved over ... samples," where the "fiber optic" embodiment has a housing shown in Fig. 35, element 3122, and the CCD-camera embodiment is shown in Fig. 30 to have a housing with a lens. Ex. 1005, 40:39-41, 35:20, Fig. 35, 30; Ex. 1002, ¶40. Gambini's optical module also has a "housing containing the light source [and] the detector." Ex. 1007, claims 12, 29; Ex. 1002, ¶40.

Artisans would have further found that the housing in all three references has an "*opening ... toward the ... wells*." Ex. 1002, ¶41. Miller's optics head has two openings in the form of objective lenses 22 (Fig. 1) and 40 (Figs. 2 and 7) through which light passes between the head and the sample wells. Ex. 1006, Figs. 1, 2 & 7; Ex. 1002, ¶41. Pantoliano's CCD camera sensor in Fig. 30 and fiberoptic sensor in Fig. 35 are shown to have a housing with an opening towards the wells for "transmitting ... excitatory light ... to samples" and "receiving spectral emission ... from samples." Ex. 1005, 35:20-24, Figs. 31, 35; Ex. 1002, ¶41. In Gambini's module, "[a]bove … the vials is a lens 2b" or "field lens 3" (lens openings) with its "focal point centered … in the vials" through which "light is passed upwardly … to a detector." Ex. 1007, 7:1-18, 8:7-12, Figs. 1-2; Ex. 1002, ¶41. Artisans would have understood that such lenses were "openings" (a term defined to include transparent materials or alternatively holes, as discussed in Petitioner's other concurrently-filed petition) and were oriented towards the samples in order to direct light onto and collect light from the samples. Ex. 1001, 6:59-64; Ex. 1002, ¶41.

Claim 1(e) and (f). Artisans would have understood that the apparatus of all three references included an "*excitation light generator*" and an "*emission light detector*." Pantoliano's device includes a generator that is a "[l]ight source 2906 [which] excites samples 2910 with excitatory light" such as a laser, and also includes a detector in the form of a "spectral receiving means or sensor" for "receiving spectral emission from the samples," such as a CCD or photomultiplier tube. Ex. 1005, 33:49-65, 34:16-23; Ex. 1002, ¶42. Miller's dual-headed detection module has two optics heads side by side (each head called a "side"), the head on one side having a "LED light source" generator and the other head having a "laser diode" generator. Ex. 1006, 1:53-67; Ex. 1002, ¶42. Each optics head within Miller's detection module also includes a "detector" within its housing. Ex. 1006, 2:30-33, 4:16-18, 5:35-38, Figs. 1-4, 7; Ex. 1002, ¶42. Gambini's optical module "compris[es] a housing containing the light source [and] the detector." Ex. 1007, claims 12, 29; Ex. 1002, ¶42.

Miller also discloses an in-head configuration in which both the light generator and the light detector are "mounted on the scan head directly" and are shown in Figs. 1-4 and 7 to be "*within the housing*" as claimed. Ex. 1006, 2:30-33, 4:16-18, 5:35-38, claims 28, 36; Ex. 1002, ¶43. For example, Figs. 1-4 and 7 depict an optics head with a housing containing a generator (*e.g.*, an LED shown as "LED" or "32", or a laser diode shown as "L/D" or "14") and detector (shown as "DET" or "in-head detectors 30 and 50"). Ex. 1006, Figs. 1-4 & 7, 6:41-45; Ex. 1002, ¶43. Gambini's optical module "compris[es] a housing containing the light source [and] the detector." Ex. 1007, claims 12, 29; Ex. 1002, ¶43. Finally, in-head placement would have been obvious in Pantoliano's device since Miller discloses that in-head placement is not only as effective as placement outside the optics head but also makes the overall device smaller, quicker and cheaper, as discussed below. Ex. 1006, Figs. 1-4, 4:16-18, 5:35-38, 2:30-33, 2:65-3:2, 1:46-49; Ex. 1002, ¶43.

Claim 1(g). Artisans would have understood that Pantoliano's and Gambini's support structures are "*attached to the thermal cycler*" – in particular, support structures such as the servo controller 3118 or filter housing 3160 are both attached to the base 3100 of Pantoliano's thermocycler. Ex. 1005, 35:6-36:2, Figs. 31-35; Ex. 1002, ¶44. Gambini's "monitoring instrument is mounted over" the "thermal cycler" block. Ex. 1007, 6:30-31, 5:25-28, Figs. 1-2; Ex. 1002, ¶44. Miller's optics head can be incoporated into any scanning device of interest, for example by attachment to a "rail" support Ex. 1006, 4:58-59; Ex. 1002, ¶44. Artisans would have understood that Miller's optics head could work effectively when attached to a cycler, since it was adapted to scan microtiter wells, the most common well format in cyclers. Ex. 1006, 3:2-5; Ex. 1011, 178A, right col.; Ex. 1002, ¶44.

Claim 1(h). Artisans would have understood that Gambini taught a cycler in which "*a heating element [wa]s disposed between the detection module and the sample wells*." Gambini discloses two heating elements – a thermal cycling block and a heated lid. Ex. 1007, 6:24-7:7, Fig. 1, 5:25-28; Ex. 1002, ¶45. Gambini further explains that sample wells should be covered "to prevent contamination and evaporation loss" during real-time monitoring by an optical system "mounted over" the sample wells. *Id*. Since this requires light transmission *through* the caps of sample tubes, Gambini's sample-tube caps are heated by a heating element "to prevent condensation under the caps" which can occlude the optical path. *Id*. Gambini's heating element is very similar to the "lid heater" of the '504 Patent: it is a "platen 2 ... over the vial caps" which is heated "sufficiently to prevent condensation under the caps," with "an array of holes 2a therethrough" that allows light to pass between the vials below and Gambini's detector above. *Id*. Like the lid heater of the '504 Patent, Gambini's platen is a heated, lid-like structure placed on top of the sample vials. *Id*. Incorporating Gambini's lid heater and Miller's optics head into Pantoliano's cycler results in the lid heater being "*disposed between*" the sample wells and optics head, as would have been apparent to artisans. Ex. 1002, ¶45.

Claim 1(i). Artisans would have understood that all three references disclose "*position[ing] the detection module in optical communication with different wells of the plurality of wells,*" and that Pantoliano and Miller further disclose that the "*shuttle is movable to position the detection module*" during scanning. Pantoliano's thermocycler contains a shuttle such as a sensor armature "used to move the sensor so that the sensor is sequentially positioned over each sample in the array of samples." Ex. 1005, 33:1-8, 35:19-35, 21:2-26, 40:39-41, Fig. 29-35; Ex. 1002, ¶46. For example, a "precision X-Y mechanism" with a "fiber-optic probe to quantify the fluorescence in each well" scans a 96-well microplate in "under one minute." Ex. 1005, 21:2-26, Fig. 29; Ex. 1002, ¶46. Similarly, Miller's optics head and associated shuttle ("support wall 60") can be "moved across a sample in two dimensions." Ex. 1006, 4:52-64; Ex. 1002, ¶46. Miller further discloses scanning "in a point-by-point imaging manner" where samples in "microtiter" plate wells are "sequentially subjected to stimulation and detection." Ex. 1006, 3:2-5, 4:52-64; Ex. 1002, ¶46. Finally, Gambini discloses that "a scanning device may be used with a single photodetector." Ex. 1007, 11:14-15; Ex. 1002, ¶46.

Claim 1(j). Artisans would have also understood from Gambini that the optics head could view the sample wells "*through a plurality of openings extending* *through the heating element*." As discussed for claim 1(h), Gambini's heating element is a heated platen with "an array of holes 2a therethrough aligned with the vials" to allow light to pass through the opaque aluminum of the platen. Ex. 1007, 6:24-7:7, Fig. 1; Ex. 1002, ¶47.

B) The third Graham inquiry: the level of ordinary skill in the art in the pertinent art and the state of the art. The knowledge of a person of ordinary skill ("artisan") was exceptionally deep and rich with respect to the claimed subject matter. The claims are directed to thermal cyclers – devices which were not merely a matter of academic interest, but part of everyday life to artisans since the advent of "end point" PCR in the mid-1980s, and of real-time PCR (*i.e*., quantitative PCR that involves optical detection during PCR) in the 1990s. Ex. 1010, 31; Ex. 1013, 17; Ex. 1012, 247; Ex. 1002, ¶16. Real-time thermal cyclers (hereafter "cyclers") were found in every lab and clinic, and typically were one of the most-used instruments there. *Id*. The claims recite features that were not only taught in the art, but were already implemented in cyclers on the market well before 2003, the effective date of the claims. In fact, artisans did not need the teachings of the applied references to recognize the various features of the claims, and to find the claims obvious.

For example, artisans already knew and used a "heating element" (claim 1) or "heater" (claim 13) with a "plurality of openings" as claimed, since such heating elements were already marketed in most cyclers. So-called "heated lids" were already in use, which were placed on sample tubes to prevent sample condensation; these heated lids started out as high-end "optional" accessories for end-point PCR instruments in the early 1990s (before real-time cyclers were on the market) to avoid condensation of the heated liquid contents onto the caps of sample tubes throughout PCR. Ex. 1014, 1; Ex. 1013, 17, 19; Ex. 1002, ¶17. Since such condensation further obstructed optical detection through the caps, heated lids became a "standard" component of real-time cyclers by the late 1990s. *Id*. The '504 Patent itself acknowledges that its "lid heater" could be of "conventional design." Ex. 1001, 5:40-41; Ex. 1002, ¶17. And because sample tubes in cyclers with metal sample blocks were typically monitored from above, through the heated lids, the lids had optical openings to let light through, just as the claims require. Ex. 1002, ¶17. Petitioner's expert is aware of at least eight prior-art references disclosing cyclers having the claimed heating element with openings. Ex. 1015, ¶46; Ex. 1016, 17:31-35; Ex. 1017, ¶112-113; Ex. 1018, 5:55-62; Ex. 1019, Fig. 1, 5:43-61; Ex. 1020, 7:8-23; Ex. 1021, 7:28-8:9; Ex. 1022, 15:18-36; Ex. 1002, ¶17.

In addition, the claimed in-head placement of optical components within the optics head itself was already found in scanning devices used to scan DNA samples on chips and microtiter wells – the most common sample-well format in cyclers. Ex. 1006, 3:2-5; Ex. 1010, 32; Ex. 1011, 178A, right col.; Ex. 1002, ¶18.

The pertinent and analogous field for fluorescence detection in real-time cyclers was the field of optical devices in general, not limited to cyclers alone. Ex. 1011, 178A, right col.; Ex. 1018, 1:53-59; Ex. 1023, 5:51-6:3; Ex. 1002, ¶18. There were historical reasons for this: cyclers were in advanced development as non-optical devices well before real-time PCR introduced optical detection into the world of cyclers in 1993. *Id*. Rather than reinventing optical systems from scratch, artisans making optical cyclers naturally looked to existing optical systems in other devices as relevant. *Id*. Real-time PCR merely required scanning or imaging of a 2D planar area, something practically any optical detector could do. Ex. 1002, ¶18. Artisans performed real-time PCR by combining non-optical thermal cyclers with a wide variety of optical devices, such as video cameras, fluorometers, plate readers and laser scanners. *Id*., Ex. 1017, ¶61; Ex. 1024, 4518; Ex. 1025, p. 3-10, Fig. 3-6; Ex. 1002, ¶18. Only the desired scanning format, rather than the nature of the sample, dictated the choice of scanner: artisans used the same scanner to scan gels, phosphorimage plates, glass slides and microtiter-well plates alike. Ex. 1006, 3:2-5; Ex. 1002, ¶18. In illustrative examples, a prior-art DNA chip reader had an optics head design taken from optical-disk devices; and a prior-art gel scanner had an optical system taken from a microscope. Ex. 1008, ¶26; Ex. 1026, 2:22-25; Ex. 1002, ¶18. Moreover, cyclers themselves were also designed to accept an equally wide variety of sample formats such as tubes, microwells, capillaries, and glass slides. Ex. 1014, 7; Ex. 1002, ¶18. Artisans thus treated the general body of optical-detection systems as pertinent and analogous art for real-time cyclers, irrespective of sample format. *Id*. Microtiter plate readers such as Miller's scan head were a natural match for cyclers since the same microtiter format was the most popular well format in cyclers, and devices which integrated thermal cyclers with plate readers were on the market by 2001. Ex. 1024, 4518; Ex. 1010, 32; Ex. 1011, 178A, right col.; Ex. 1002, ¶18. Since optics heads had already been designed to scan microtiter wells in other devices, it was only a matter of time – not inventiveness – before these optics heads were used in cyclers as well. Ex. 1002, ¶18.

C) Rationales for obviousness. Pantoliano's thermocycler meets all limitations of the challenged claims except for two predictable features: (1) in-head placement of the generator and detector – a known configuration for optics heads taught by Miller, and (2) a heater with optical holes – a standard component of real-time thermocyclers, taught for example by Gambini. Ex. 1002, ¶48. The combination of Pantoliano, Miller and Gambini rendered claim 1 obvious by several independent rationales.

Teachings to combine within the applied references: The references themselves provided strong incentives to combine. Ex. 1002, ¶49. In Pantoliano's 1997 thermocycler, the source and detector were too big to fit inside the optics head itself, making in-head placement undesirable since the optics head would be slowed down by the "high mass" of such large components. Ex. 1006, 1:16-19; Ex. 1002, ¶49. But by the '504 Patent's priority date of 2003, technology had progressed apace: light generators and detectors had become both smaller and more powerful, making placement in-head not only viable but very attractive. Ex. 1006, 2:65-3:2; Ex. 1008, ¶79; Ex. 1028, Fig. 10, 11:24-34; Ex. 1029, Fig. 1, col. 3; Ex. 1002, ¶49. For example, Miller recognized in 2000 that in-head placement was not only as effective as placement outside the optics head, but also resulted in making the overall device smaller, quicker and cheaper. Ex. 1006, Figs. 1-4, 4:16-18, 5:35-38, 2:30-33, 2:65-3:2, 1:46-49; Ex. 1002, ¶49. In particular, Miller emphasized that "incorporating ... [optical] elements into a compact scan head and moving the scan head, as opposed to moving a scanning mechanism within the optical system" resulted in a system that was more "light weight, high speed, and extremely versatile," and had a "low cost design" since it eliminated components such as optical fibers. *Id*. The '504 claims were apparently allowed because in-head placement was alleged to be a "significant advantage" over Pantoliano's fiber-optic design. Ex. 1004, p. 27:23-24; Ex. 1002, ¶49. Miller recognized this advantage well before the '504 Patent, and thus provided strong incentive to combine. Ex. 1002, ¶49.

It would have further been obvious to include a "heating element" with "openings" as required by claim 1. As discussed for the state of the art, this element was already a "standard" compenent in real-time cyclers; its "conventional design" is acknowledged by the '504 Patent. Ex. 1014, 1; Ex. 1013, 17, 19; Ex. 1001, 5:40-41; Ex. 1002, ¶50. It is not surprising that this feature was omitted from the claims during ten years of prosecution, and only added just prior to issuance in order to create a nominal difference over the cited art which happened to lack mention of heated lids (including a related Pantoliano patent US6569631). Ex. 1004, 22-27; Ex. 1027, 44:43-45; Ex. 1002, ¶50. Viewed in the proper perspective, however, the recitation of a heating element is a distinction without a difference. Since heated lids were not only well known but ubiquitous in cyclers, the absence of a heated lid in a cycler may conceivably have been inventive; its presence was certainly not. To boot, Gambini explained that heated lids addressed the well-known problem of sample condensation endemic to cyclers since the advent of PCR, which obstructed a view of sample-tubes' contents. Ex. 1007, 7:3-7; Ex. 1002, ¶50. And because sample tubes in real-time machines were often monitored *through* the heated lids, heated lids could have openings to allow light through, as Gambini and Patentee's own prior art noted. *Id*., Ex. 1021, 7:28-8:9; Ex. 1002, ¶50. Artisans thus would have found it obvious to include a heating element (such as

Gambini's heated lid) in Pantoliano's cycler equipped with Miller's optics head, so it could view samples more clearly.

Predictable combination of known elements: The claimed devices are merely a combination of known elements with predictable results, since Miller's optics head and Gambini's heated lid could be included in Pantoliano's cycler with no change in their functions, with entirely predictable results. Miller expressly recognized that placement of the generator/detector inside the optics head was functionally equivalent to placement outside the head: specifically, Miller taught that the detector could be included in the housing of the optics head, "or in a remote location and connected ... via an optical fiber." Ex. 1006, 2:30-33, Figs. 1-4, 7; Ex. 1002, ¶51. In the face of such recognized equivalence, it would have been obvious to include Miller's optics head in Pantoliano's cycler. Similarly, Gambini's heated lid had openings to ensure that the performance of an optics head would be unaffected. And both Miller's scan head and Gambini heated lid were designed for samples in microtiter wells just as Pantoliano's thermal cycling block also was. Ex. 1006, 3:2-5; Ex. 1005, 16:15-18; Ex. 1007, 6:22-23; Ex. 1002, ¶51. Thus, artisans would have clearly understood that combining Miller's optics head and Gambini's heated lid with Pantoliano's cycler was merely a matter of routine combination with entirely predictable results. Ex. 1002, ¶51.

Design incentives and other market forces: Even if the applied references had lacked suggestions to combine, there were design incentives to do so. Ex. 1002, ¶52. As one review noted, a "small footprint," low cost, and short amplification time were critical selling points in the "cut-throat" business of cyclers. Ex. 1014, 1-2; Ex. 1002, ¶52. Artisans would thus have been quick to note that Miller's optics head provided exactly these advantages: it was expressly "compact" and "light weight, high speed, and extremely versatile" with a "low cost design," and designed with "[s]pace and cost considerations" in mind. Ex. 1006, 2:65-3:2, 1:31-49; Ex. 1002, ¶52.

Another design incentive was that Miller's scan head avoided known drawbacks of the fiber-optic design of Pantoliano's sensor: detection with optic fibers was less reproducible because "light communication efficiency ... changed" as fibers bent during scanning, "move range [wa]s limited ... [by] bendability," and fibers were prone to breakage. Ex. 1030, 2:56-84; Ex. 1002, ¶53. In particular, it was known that "movement" of fiber optic probes like Pantoliano's slowed down head movement, produced "stresses that cause mechanical failure" and caused the "curvatures of the light-transmitting fibers [to] change, introducing variations in their optical properties," thereby creating "inconsistencies in readings between different wells and adversely affect[ing] the repeatability, and thus, accuracy of measurements." Ex. 1031, 2:15-41; Ex. 1002, ¶53.

Thus, artisans already understood that mounting "light source(s) and detector(s) ... at the optics head" was desirable since it resulted in "eliminating the cost and light loss associated with fiber optics." Ex. 1032, 7:3-10; Ex. 1002, ¶54. Patent Owner itself affirmed in prosecution that it was "well known in the art [that] deforming a fiber changes its optical transmission properties" and gained allowance by arguing that in-head placement provided a "significant advantage" since the "optical path ... does not vary" during scanning. Ex. 1004, p. 27:15-24; Ex. 1002, ¶54. What Patent Owner failed to acknowledge was that in-head placement, which avoided the drawbacks of fiberoptic cables, was already a well-known design choice for optics heads. Ex. 1002, ¶54. Miller's "dual-head" format, with two different generators (both LED and laser) providing "multiple scanning modalities," was yet another design incentive: as the '504 Patent acknowledges, multiplex monitoring capability of "different fluorescent probes" was a desired feature in a cycler. Ex. 1006, 1:53-2:1; Ex. 1001, 11:31-38; Ex. 1002, ¶54. Such design incentives would have further prompted artisans to switch to Miller's optics head in Pantoliano's cycler.

There was also strong design incentive to include Gambini's heated lid in Pantoliano's cycler. Pantoliano's outmoded method of oil overlay to prevent condensation was disfavored by customers: not only was it cumbersome and messy, it also caused variability due to "added thermal mass" and "reduced the fluorescent signal detected." Ex. 1005, 43:37-39; Ex. 1037, 544; Ex. 1002, ¶55. Because "oil-free" cycling made possible by heated lids was much preferred, there was market incentive to use Gambini's heated lids, which thus became ubiquitous in cyclers by 2001. Ex. 1013, 17, 19; Ex. 1002, ¶55.

Reasonable Expectation of Success. Artisans had a reasonable expectation of success in arriving at the apparatus of claim 1 by combining Pantoliano, Miller, and Gambini. Ex. 1002, ¶56. All three references taught that their respective components could be successfully used for the claimed purposes. Pantoliano's apparatus was a fully-functioning cycler for "polymerase chain reaction [and] thermal cycling" that was "capable of scanning 96 samples in under one minute," fast enough for real-time PCR. Ex. 1005, 42:57-62, 21:18-19; Ex. 1033, p133; Ex. 1002, ¶56. Miller's optics head was effective for "point-by-point" and "rapid" scanning; and Gambini's heated lid was effective to "prevent condensation ... without interfering with DNA replication in" sample wells. Ex. 1006, 4:52-64, 1:46-49; Ex. 1007, 6:24-7:7; Ex. 1002, ¶56.

An artisan simply needed to incorporate Miller's optics head, and Gambini's heated lid, into Pantoliano's cycler according to the guidance provided by these references. Pantoliano's shuttle could be adapted for a variety of sensors ranging from fiber optics to CCD cameras, and could routinely accommodate Miller's "compact" optics head. Ex. 1005, Figs. 31, 33, 35:19-35; Ex. 1002, ¶57. The '504

Patent itself treats the shuttle as merely part of an "exemplary apparatus" and thus optional, and the attachment of the optics head to the shuttle as routine. Ex. 1001, 4:7-15, 2:60-65; Ex. 1002, ¶57. The components supplied by all three references were mutually compatible, being designed for use with samples in "microtiter" wells, or more specifically "96 [wells] in an array of 12 by 8." Ex. 1006, 3:2-5; Ex. 1005, 16:15-18; Ex. 1007, 6:22-23; Ex. 1002, ¶57.

Moreover, it was known that cyclers had "better accuracy and precision" when they scanned "samples individually and sequentially," even though some "optical variation" was caused by moving parts. Ex. 1011, p. 177-78, Table 1; Ex. 1002, ¶58. Thus, various cyclers on the market used movable "scanning systems" such as "scanning heads" to scan wells, and routinely addressed any optical variation by using a calibration element, just as taught by both Pantoliano and Gambini (see claim 3). *Id.*

Thus, claim 1 merely combines Pantoliano's scanning cycler with prior-art features known to improve scanning. There was already strong incentive to do so, and in any event the combination was routine with only predictable results. Ex. 1002, ¶59. Accordingly, claim 1 would have been obvious.

Independent Claim 13 (preamble) and (a). As discussed already for claim 1(preamble) and (a), artisans would have understood that the combination cycler was a "*thermal cycler apparatus comprising a thermal cycler having … a plurality* *of sample wells for holding reaction vessels*" as required by claim 13(preamble) and (a). Pantoliano's apparatus is a cycler which can be "used to perform polymerase chain reaction, [or] thermal cycling steps for any purpose" since the "temperature of heat conducting block ... can be increased, decreased, or held constant," and the block includes "a plurality of wells ... for a plurality of samples" in "containers" such as "tubes" or "microtiter" wells. Ex. 1005, 42:57-62, 35:43-61, 33:37-40, 16:15-17; Ex. 1002, ¶60. And Gambini discloses a thermal cycler, as an "optical instrument ... for monitoring polymerase chain reaction" with "fluorescent" dyes in a "thermal cycler block for holding at least one vial." Ex. 1007, 2:18-22, Fig. 1; Ex. 1002, ¶60.

It would also have been obvious that the combination cycler had "*an exterior housing*" as claim 13(a) states. Pantoliano's cycler has an exterior "housing 3400 that covers the apparatus," shown in Figs. 34 and 35. Ex. 1005, 39:37-39, Fig. 34, 35; Ex. 1002, ¶61. Miller's movable optics head is part of (and thus housed within) an "optical scanner" that can scan "microtiter" wells. Ex. 1006, 1:6-8, 1:46-49, 3:2-5; Ex. 1002, ¶61. Gambini's "optical instrument ... for monitoring polymerase chain reaction" is "incorporated into" a cycler. Ex. 1007, 2:18-28, 5:18, Fig. 1; Ex. 1002, ¶61. It was obvious that these apparatus had exterior housings, which were required to prevent ambient light from interfering with detection. Ex. 1002, ¶61.

Claim 13(b). As discussed for the "heating element" in claim 1(h), artisans would have understood that the combination cycler had a "*heater to prevent condensation from forming on ... the reaction vessels when ... in the sample wells*." Gambini discloses a heating "platen 2 rests over the vial caps" with "an array of holes 2a therethrough aligned with the vials," where the platen is heated "sufficiently to prevent condensation under the caps." Ex. 1007, 7:1-5, Fig. 1; Ex. 1002, ¶62.

Claim 13(c). As discussed already for claim 1(j), artisans would have understood that the heater had "*transparent portions to permit optical communication with each of the ...wells*." Gambini's heated platen has "an array of holes 2a therethrough aligned with the vials" and above these is a "field lens 3" oriented towards the wells," so that an "excitation beam is focused … into the center of the vials" through the holes "into the center of the vials," from where "light is passed upwardly … to a detector." Ex. 1007, 7:1-5, 8:7-12, Fig. 1; Ex. 1002, ¶63. Claim 22, which depends from claim 13, makes clear that the so-called "transparent portions" of claim 13(c) can be holes like those found in Gambini's heated lid.

Claim 13(d). As discussed already for claim 1(b), artisans would have understood that the combination cycler had "*a support structure,*" and that the support is "*disposed inside the exterior housing*" of the cycler. Pantoliano's support structures such as the servo controller 3118 or filter housing 3160 are all situated within an exterior "housing 3400 that covers the apparatus," shown in Figs. 34 and 35. Ex. 1005, 39:37-39, Figs. 34, 35; Ex. 1002, ¶64. Miller's movable optics head is part of (and thus housed within) an "optical scanner." Ex. 1006; Ex. 1002, ¶64. Gambini's "optical instrument ... for monitoring polymerase chain reaction" is "incorporated into" (and thus housed within) a cycler. Ex. 1007, 2:18-28, 5:18, Fig. 1; Ex. 1002, ¶64. Artisans would have recognized through common sense that these apparatus had exterior housings to prevent ambient light from interfering with detection. Ex. 1002, ¶64.

Claim 13(d) further specifies that the support is "*on an opposite side of the heater from the ... wells*." Gambini's heated platen "rests over" the sample wells, at the "bottom" of the monitoring system which supports an optical train; this monitoring system is "mounted over" the cycling block, *i.e.*, placed above the wells. Ex. 1007, 6:30-7:7; Ex. 1002, ¶65. Incorporating Gambini's lid heater as instructed (*i.e*, on top of the sample wells, under the detection system's support) results in the support being on top of the heater, and "*on an opposite side of the heater from the ...wells*." Ex. 1002, ¶65. Pantoliano's support structures such as "relative movement means 3130," "sensor armature servo controller 3118," "filter housing 3160" are aligned with the shuttle situated above the wells as shown in Figs. 31-35, and thus would be on an opposite side of the heater from the wells, as discussed for claim 1(b) and (h). Ex. 1005, Figs. 31-35, 35:6-36:2; Ex. 1002, ¶65. Other supports such as movement means 3316 and lid 3400 (connected to base 3100) are at least partly on an opposite side from the wells. Ex. 1005, Fig. 33, 35; Ex. 1002, ¶65. The '504 Patent itself discloses a support that is only partly on the opposite side of the heater from the wells: the "[l]ower portions of supports" extend through the lid heater in Fig. 2 in order to "compress lid heater ... towards sample unit" and are thus not on the opposite side from the wells. Ex. 1001, 5:9-12; Ex. 1002, ¶65.

Claim 13(e). As discussed already for claim 1(b), artisans would have understood that the combination cycler had a "*shuttle movably mounted on the support structure*."

Claim 13(f). As discussed already for claim 1(c) and (d), artisans would have understood that the combination cycler had a "*detection module attached to the shuttle ... including a module housing having an opening ... oriented toward the ...wells when the thermal cycler is ... operating*."

Claim 13(g) and (h). As discussed above for claim 1(e) and (f), artisans would have understood that the combination cycler had an "*excitation light generator*" and an "*emission light detector*."

As also discussed for claim 1(e) and (f), Miller discloses in-head placement in which both these components are "*disposed entirely within the module housing*."

As shown in Figs. 1-4, Miller's generator and detector are placed within the optics head housing. Ex. 1006, Figs. 1-4 and 7, 1:53-56; Ex. 1002, ¶69.

Claim 13(i). As discussed for claim 1(i) and (j), artisans understood that the "*shuttle is movable to position the detection module in optical communication with different sample wells ... through the transparent portions of the heater*."

The rationales for obviousness discussed above for claim 1 at the beginning of this Ground apply equally to claim 13. There was moreover strong reason to ensure that the combination cycler had "*an exterior housing*" and that the optics head's support was "*disposed inside the exterior housing*." It was well known that a cycler needed an opaque exterior housing in order to ensure that its contents and in particular the sample wells were "light-sealed to prevent external light sources from influencing fluorescence detection." Ex. 1017, ¶59; Ex. 1002, ¶71. In addition, there was strong reason "*to prevent condensation*" of the sample as claimed in real-time cyclers that monitored samples through a surface of the sample tube; this surface had to be "heated so that condensation from the reaction mixture does not form in the optical pathway" of collected light signals, leading to "variability ... due to scatter and/or absorption." Ex. 1019, 2:57-65; Ex. 1002, ¶71.

Finally, there was reason to ensure that the optics head and thus its support would be "*on an opposite side of the heater from the ...wells*." Gambini's heated lid required direct contact with the sample tube tops in order to heat them effectively and prevent condensation, and included optical holes to allow light through when the heated lid was placed between the wells and the optics head. Ex. 1007, 6:24-7:7; Ex. 1002, ¶72. Thus there were strong reasons for the heated lid to be placed such that the optics head support and the wells were on opposite sides of the heated lid. Ex. 1002, ¶72.

Artisans had a reasonable expectation of successfully incorporating Miller's optics head and Gambini's heated lid into Pantoliano's cycler, for at least the reasons discussed for claim 1. And Pantoliano's cycler already had an exterior housing, requiring no further effort in making the combination. Ex. 1002, ¶73. Thus, claim 13 would have been obvious.

Claims 2 and 20. Claims 2 and 20 recite the apparatus of claims 1 and 13 respectively, wherein an "*excitation optical path from the ... generator to the opening*" of the optics head and a "*detection optical path from the opening to the ... detector*" both have "*a fixed length*" (claim 2) or are both defined by "*a plurality of optical components*" for light of an excitation or detection wavelength, wherein "*all of the optical components ... are disposed within the housing*" of the optics head (claim 20). Base claims 1 and 13 would have been obvious as discussed above. Further, Miller's optics head is self-contained and "supports two or more optical systems within a small space" such that all optical components are affixed to the "support wall" of the optics head which "provides the physical support for the various elements." Ex. 1006, 1:55-56, 2:49-51, Figs. 1-4, 7; Ex. 1002, ¶74. Being in fixed positions, these optical components define an optical path of fixed length as required by claim 2; and as shown in Figs. 1 and 2, all these optical components are contained within the housing of the optics head as required by claim 20. Ex. 1002, ¶74. Thus, claims 2 and 20 were obvious. The rationales for obviousness and expectation of success already discussed in this Ground for base claims 1 and 13 apply equally to claims 2 and 20, which thus were obvious. Ex. 1002, ¶74.

Claim 3. Claim 3 recites the apparatus of claim 1, further comprising "*a calibration element disposed such that the detection module is movable so as to be positioned in optical communication with the calibration element, wherein the calibration element provides a known fluorescence response*." Base claim 1 was obvious as discussed above. And both Pantoliano's and Gambini's cyclers contain a calibration element, common in cyclers. Ex. 1002, ¶75. Pantoliano's calibration element ("CE") is an "aliquot of ... [known analyte] of known concentration" which thus provides a known fluorescence response, which is placed in a "control container" such as "a well of a multiwell microplate," so that the optics head can move into view of it. Ex. 1005, 28:19-23; Ex. 1002, ¶75. Gambini's calibration element is a "fluorescent reference member 4 that emits reference light in response to the excitation beam," which is "disposed to receive a portion of the excitation beam" close to the sample wells (*see, e.g*., Fig. 4, element 4), so that "fluorescence data are taken" from the samples and CE together; the reference member "generate[s] reference signals for utilization along with the data signals in the computing of the concentration of DNA." Ex. 1007, 11:24-12:4, 13:5-7; Ex. 1002, ¶75.

The reasons for obviousness and expectation of success discussed above for base claim 1 apply equally to claim 3. There was further reason to use a calibration element because Gambini taught it "corrects for instrument drift during the monitoring." Ex. 1007, 15:7; Ex. 1002, ¶76. Thus, claim 3 would have been obvious. Ex. 1002, ¶76.

Claims 6, 7 and 19. Claims 6, 7 and 19 recite the apparatus of claims 1 and 13 respectively, wherein an "*external computer*" controls the "*positioning of the detection module with respect to the wells*" (claim 6), or the "*operation of the ... generator and ... detector*" (claim 7), or both the "*movement of the shuttle and operation of the ... generator and the ... detector ... such that emission light is measured while the shuttle is in motion*" (claim 19). Base claims 1 and 13 were obvious as discussed above. And in Pantoliano's cycler the "excitatory light source" (generator), the "photomultiplier tube" (detector) and the "sensor armature" (shuttle), are all controlled by corresponding servo controllers which in turn are controlled by a corresponding computer controller. Ex. 1005, 36:1-50, Figs. 29-35;

Ex. 1002, ¶77. Specifically, computer controller 3142 "controls the movement of sensor armature [*i.e.*, shuttle]" via servo controller 3118, a second computer controller 3102 "controls the wavelength of excitatory light transmitted to sample" via servo controller 3106, and a third computer controller 3170 controls the "spectral emission servo controller 3112." *Id*. In turn, these computer controllers can be "implemented using one or more computer systems such as computer system 3702," or a computer controller (*e.g*., 3142) could be dispensed with and an external "computer 2914 could be used to control [a] servo controller" directly. Ex. 1005, 41:25-28, 35:17-18, Figs. 29-35; Ex. 1002, ¶77. It thus was obvious to use an external computer to control the shuttle, generator and detector as claimed. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 6, 7 and 19, which thus were obvious also. Ex. 1002, ¶77.

Claim 8. Claim 8 recites the apparatus of claim 1, wherein "*the detection module is detachably attached to the shuttle*." Base claim 1 was obvious as discussed above. Further, Pantoliano's sensor (*e.g*., a fiber optic probe or CCD camera) is "removably attached to the sensor armature [*i.e*., shuttle]." Ex. 1005, 35:19; Ex. 1002, ¶78. The reasons for obviousness and expectation of success discussed above for base claim 1 apply equally to claim 8. There was further reason to make the sensor module detachable for easier repair and replacement, and to allow users a choice of optics head tailored to a particular assay. Claim 8 thus was obvious. Ex. 1002, ¶78.

Claims 9 and 14. Claims 9 and 14 recite the apparatus of claims 1 and 13, wherein the "*generator comprises a light-emitting diode*." Base claims 1 and 13 would have been obvious as discussed above. Further, Miller's dual-sided optics head contains a "light emitting diode (LED)" as generator on one side, and a laser generator on the other side, teaching their equivalence as light sources within an optics head. Ex. 1006, 1:64-67; Ex. 1002, ¶79. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 9 and 14. Miller also discloses that LED sources were an "inexpensive alternative" to other light sources such as lasers and were "particularly useful for certain specified wavelengths," providing further incentive to use LEDs in an optics head. Ex. 1006, 5:46-48; Ex. 1002, ¶79. Claim 9 and 14 thus were obvious. Ex. 1002, ¶79.

Claim 10 and 15. Claims 10 and 15 recite the apparatus of claims 1 and 13, further comprising "*at least two stepper motors mounted on the support structure, the stepper motors being operative to move the shuttle in at least two dimensions*." Base claims 1 and 13 were obvious as discussed above. Further, Pantoliano's sensor armature (shuttle) is moved by a "relative movement means" in one direction, of which two in combination can form a "precision X-Y mechanism" for

2-D movement, and the movement means can be controlled by a motor. Ex. 1005, 35:65-36:11, 21:11-13; Ex. 1002, ¶80. Similarly, Miller's optics head and shuttle ("support wall 60") can be "moved across a sample in two dimensions," by means that are "motorized." Ex. 1006, 4:52-64; Ex. 1002, ¶80. The exact choice of motor as a "stepper" motor was a routine design choice within the skill of an artisan; the '504 Patent acknowledges that the stepper motor was of "conventional design" and that "other types of motors, such as servo motors or linear motors, may also be used" instead. Ex. 1001, 6:14-25; Ex. 1002, ¶80. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 10 and 15, which thus were obvious. Ex. 1002, ¶80.

Claim 11 and 17. Claims 11 and 17 recite the apparatus of claims 1 and 13, wherein "*the detection module includes at least two ... detectors*." Base claims 1 and 13 would have been obvious as discussed above. And artisans knew, as evidenced by Miller, the benefits of a 'dual-head' configuration, in which two individual optics heads, each with a separate generator and detector, are enclosed together within the same housing side by side to form a single (composite) detection module. Ex. 1006, Figs. 1-4; Ex. 1002, ¶81. Miller's two-headed module could advantageously monitor two different wavelengths simultaneously, allowing multiplexed analysis – a highly desired feature in cyclers, as the '504 Patent acknowledges. Ex. 1006, 1:64-2:1; Ex. 1014, p. 2; Ex. 1001, 11:31-39; Ex. 1002,

¶81. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 11 and 17. Claims 11 and 17 thus were obvious. Ex. 1002, ¶81.

Claim 16. Claim 16 recites the apparatus of claim 13, further comprising "*a fitting on an exterior surface of the housing of the detection module, the fitting adapted to attach the detection module to the shuttle, wherein the fitting provides only electrical and mechanical connections*." This claim merely recites a routine design choice, and the Patent Office has correctly recognized that this limitation does not serve to distinguish the claims from the art. Ex. 1004, 45 (rejecting claim 19 reciting such a fitting for the same reasons as base claim 16); Ex. 1002, ¶82. Artisans were already familiar with appropriate fittings which provided mechanical or electrical connections between a detachable optics head and a shuttle. For example, Ackley disclosed a scanner with an "optical sensor module 20" (optics head) which "comprises a generally rectangular housing [i.e., fitting] that fits snugly within a corresponding receptacle" of a scan head (shuttle), with a "bore provided in a portion of the housing to secure the sensor module 20 to the scan head 14" (i.e., mechanical connection), and "connector 22 of the sensor module 20 to provide an electrical connection between the sensor module 20 and the other elements of the scanner." Ex. 1034, 4:45-67; Figs. 2-4, 2:63-3:21; *see also* Ex. 1035, 6:47-67; Ex. 1031, cols. 6-7; Ex. 1002, ¶82. The reasons for obviousness and expectation of success discussed for base claim 13 apply equally to claim 16. Moreover, Miller's optics head needed electrical connections to power and control its internal light generator and detector, and also needed mechanical connections for stable attachment to a movement means, giving artisans ample reason to provide the optics head with the fitting of claim 16.

Claim 22. Claim 22 recites the apparatus of claim 13, "*wherein the plurality of transparent portions of the heater includes a plurality of holes extending through the heater and aligned with the sample wells*." As discussed, Gambini's heated platen includes "an array of holes 2a therethrough aligned with the vials" (*i.e.*, sample wells), in order to allow light to pass through the opaque aluminum of the platen. Ex. 1007, 7:2, Fig. 1; Ex. 1002, ¶83. The reasons for obviousness and expectation of success discussed above for base claim 13 apply equally to claim 22, which thus was obvious. Ex. 1002, ¶83.

VII. Ground 2: Claim 21 would have been obvious in view of Pantoliano, Miller, Gambini and Li under pre-AIA §103(a)

Claim 21 recites the apparatus of claim 13, "*wherein the detection module is positioned such that the opening is below the plurality of sample wells*." Base claim 13 was obvious over Pantoliano, Miller and Gambini, as discussed above. Claim 21 was similarly obvious in view of Li. Ex. 1039, Ex. 1040. Li discloses a cycler with an optics head substantially similar to Miller's, where as shown in Fig. 3, Li's optics head and its opening are positioned "*below the plurality of sample* *wells*" as required by claim 21. Ex. 1040 at 8:16-20, 8:28-9:1, Fig. 3; Ex. 1002, ¶85. The reasons for obviousness and expectation of success discussed above for base claim 13 in Ground 1 apply equally to claim 21, which thus was obvious. Ex. 1002, ¶85.

VIII. Ground 3: Claims 1-3, 6-7, 10, 13, 15-16, 19, 20 and 22 would have been obvious in view of Iwasaki, Pantoliano and Gambini under pre-AIA §103(a)

As shown below, claims 1-3, 6-7, 10, 13, 15-16, 19, 20 and 22 would have been obvious over the combination of Iwasaki, Pantoliano and Gambini. The references together disclosed all elements of the claims, and there were many reasons to combine their teachings, making the claims obvious by their asserted priority date of 2003. Iwasaki disclosed a self-contained optics head used to scan an array of DNA samples, Pantoliano disclosed a thermal cycler with a scanning sensor on a shuttle and support, and Gambini disclosed a heating element with openings for use in a thermal cycler. A detailed *Graham* analysis is provided below for representative claim 1 and is also applicable to the other claims as well. *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

A) The first two *Graham* inquiries: Determining the scope and content of the prior art and ascertaining the differences from the claims: The scope and content of the art is such that there are no real differences between the challenged claims and the art; the combination of Iwasaki, Pantoliano and Gambini discloses all elements of the claims, except for their combination together. Representative claim 1 is directed to a fluorescence detection apparatus with an optical detection module ("**optics head**") that can be moved to view different sample wells, containing a light generator and detector placed within the housing of the optics head ("**in-head**") instead of outside it. Iwasaki discloses such an optics head for scanning DNA samples. Ex. 1002, ¶88. Claim 1 also requires that (1) the optics head is attached to a movable shuttle on a support within a thermal cycler ("cycler") as disclosed by Pantoliano, and (2) the cycler has a heating element with openings to allow scanning, as taught by Gambini. Ex. 1002, ¶88.

Independent claim 1: The combination of Iwasaki, Pantoliano and Gambini discloses all elements of claim 1, as discussed below.

Claim 1 (preamble). As Professor Mathies explains, a person of ordinary skill in the art ("**artisan**") would have understood that all three references disclose a "*fluorescence detection apparatus,*" and that Pantoliano and Gambini disclose apparatus "*for analyzing samples ... in ... wells in a thermal cycler*." Iwasaki discloses an optics head termed a "reading head" which is used as a "DNA chip reader" for detecting "fluorescence generated by a DNA chip." Ex. 1009, Abstract, claim 1; Ex. 1002, ¶90. As discussed in Ground 1 for this claim element, Pantoliano and Gambini disclose optics heads for analyzing "*samples ... in ... wells in a thermal cycler*" as further recited in claim 1 (preamble).

Claim 1(a). Artisans would have understood that all three references taught or suggested "*a support structure attachable to the thermal cycler*." Iwasaki's optics head is within a "scanning device" mounted over a sample fixed to a sample stage, which includes a support in the form of an "X-axis guide rail 3 and an X-axis worm gear 5 ... arranged on both sides of the sample stage" (Fig. 6), and it would have been obvious that this support was attachable to a thermal cycler. Ex. 1009, ¶72, Fig. 6; Ex. 1002, ¶91. As discussed in Ground 1 for this claim element, Pantoliano and Gambini also disclose this feature.

Claim 1(b). Artisans would have understood that Iwasaki discloses or at least suggests a "*shuttle movably mounted on the support,*" and further that Pantoliano discloses and Gambini suggests this feature as well. Iwasaki discloses that a "Y-axis worm gear 6 is arranged on the X-axis guide rails 3 ... and this is driven in the X-axis direction by the motor 4," and that a "motor 7 is connected to the Y-axis worm gear 6, and ... is activated to scan what is fixed to the Y-axis worm gear 6." Ex. 1009, ¶73, Fig. 6; Ex. 1002, ¶92. Artisans would have understood that the Y-axis worm gear, for example the site of attachment of the optics head to the Y-axis worm gear, was a shuttle that was movably mounted on the X-axis guide rail supports. Ex. 1002, ¶92. In any event, Pantoliano discloses and Gambini suggests this feature, as discussed in Ground 1 for this claim element.

Claim 1(c). Artisans would have understood that all three references disclose a "*detection module*" ("**optics head**"), which is further "*attached to the shuttle*" in Pantoliano and Miller. Iwasaki's detection module is a "reading head 8 containing reading optics" which "is attached to a Y-axis worm gear 6" (shuttle). As discussed in Ground 1 for this claim element, Pantoliano and Gambini also disclose this feature. Ex. 1002, ¶93.

Claim 1(d). Artisans would have understood the detection modules ("**optics head**") of all three references had a "*housing*." Iwasaki's "DNA chip reading head is housed inside a single case 26." Ex. 1009, ¶55, Fig. 6; Ex. 1002, ¶94. As discussed in Ground 1 for this claim element, Pantoliano discloses and Gambini suggests this feature.

Artisans would have further found that the housing in all three references has an "*opening ... toward the ... wells*." Ex. 1002, ¶95. Iwasaki discloses that an opening in the form of an "aspherical objective lens 14" that is fixed within the housing (Fig. 1), through which light "is focused ... on a DNA chip" containing the arrayed samples. Ex. 1009, ¶49, Fig. 1; Ex. 1002, ¶95. Although Iwasaki's samples are not in wells, Pantoliano and Gambini also disclose the use of optics heads with openings oriented towards sample wells in cyclers, as discussed in Ground 1 for this claim element.

Claim 1(e) and (f). Artisans would have understood that the apparatus of all three references included an "*excitation light generator*" and an "*emission light detector*" that are "*disposed within the housing*" of the optics head. Ex. 1002, ¶96. Iwasaki's reading head includes a laser beam "semiconductor light source 11" (generator) and an "integrated fluorescence intensity measuring sensor" such as "light-receiving element 20" (detector) that are both "arranged inside a single case" *i.e.*, within the head's housing as shown in Fig. 1. Ex. 1009, ¶¶49, 17, 52, 27, claim 1, Fig. 1; Ex. 1002, ¶96. As discussed in Ground 1 for this claim element, Pantoliano and Gambini also disclose this feature.

Claim 1(g). As discussed in Ground 1 for this claim element, artisans would have understood that Pantoliano's and Gambini's support structures are "*attached to the thermal cycler*." In addition, Iwasaki's support was a generic "X-Y scanning" mechanism compatible with thermal cycler; Pantoliano explains that the same "X-Y mechanism" can scan microplate wells in a thermal cycler. Ex. 1009, ¶28; Ex. 1005, 21:3-26; Ex. 1002, ¶97.

Claim 1(h). As discussed in Ground 1 for this claim element, artisans would have understood that Gambini discloses a cycler in which "*a heating element [wa]s disposed between the detection module and the sample wells*."

Claim 1(i). Artisans would have understood that all three references disclose "*position[ing] the detection module in optical communication with different wells* *of the plurality of wells,*" where the "*shuttle is movable to position the detection module*" during scanning. Due to its two worm gears, Iwasaki's "reading head 8 can scan ... in the X and Y directions," where the head "is moved a single pitch" at a time where the "dimension of a single pitch is selected so that all of the [samples] on the DNA chip can be measured." Ex. 1009, ¶75; Ex. 1002, ¶99. As discussed in this Ground for claim 1(b), Iwasaki's Y-axis worm gear, for example the site of attachment of the optics head to the Y-axis worm gear, acts as a shuttle that is movably mounted on the X-axis guide rail supports, and this shuttle positions the reading head during scanning. Ex. 1002, ¶99. As also discussed in Ground 1, Pantoliano and Gambini also disclose this feature.

Claim 1(j). As discussed in Ground 1 for this claim element, artisans would have also understood from Gambini that the optics head could view the sample wells "*through a plurality of openings extending through the heating element*."

B) The third Graham inquiry: the level of ordinary skill in the art in the pertinent art. As already discussed in Ground 1, the knowledge of a person of ordinary skill ("artisan") was exceptionally deep and rich with respect to the claimed subject matter. As discussed in Ground 1, heating elements with openings were already a standard component of thermal cyclers. Since optics heads had already been designed to scan microtiter wells in other devices, it was only a matter of time – not inventiveness – before these optics heads were used in cyclers as well. In fact, they already had been. Ex. 1040, 8:16-9:7; Ex. 1028, 11:24-34, Fig. 10; Fig. 3; Ex. 1002, ¶18.

C) Rationales for obviousness. Iwasaki's optics head meets all limitations of the claimed "detection module," except that Iwasaki uses this optics head as an array reader for DNA chips, and not for sample wells in a thermal cycler. Pantoliano discloses that an optics head can be mounted on a movable shuttle attached to a support in order to scan wells in a thermal cycler. Gambini discloses the use of a heating element as claimed in a thermal cycler.

Iwasaki's optics head can be combined with Pantoliano's cycler in two different ways to arrive at the claimed subject matter. First, Iwasaki's optics head and X-Y scanning apparatus, which as discuss in claim 1(b) includes a shuttle (Y-axis worm gear) and a support (X-axis guide rail), can be mounted onto Pantoliano's cycling block. Alternatively, Iwasaki's optics head can be mounted on Pantoliano's shuttle and support, in a similar manner to Miller's optics head discussed in Ground 1 above. It was obvious to combine Iwasaki, Pantoliano and Gambini in the claimed manner by several independent rationales.

Teachings to combine within the applied references: The references themselves provided strong incentives to combine. In Pantoliano's 1997 cycler, the source and detector were too big to fit inside the optics head itself, making 'in-head' placement undesirable since the optics head would be slowed down by the "high mass" of such large components. Ex. 1006, 1:16-19; Ex. 1002, ¶103. But as already discussed in more detail in Ground 1, technology had progressed apace: by the '504 Patent's priority date of 2003, generators and detectors had become both smaller and more powerful, making placement in-head not only viable but very attractive. Ex. 1002, ¶103. For example, Iwasaki's optics head with in-head placement had a "very compact and lightweight" design which reduced "manufacturing costs" and allowed the overall device to be "portable" for "onsite DNA analysis in clinics and customs offices." Ex. 1009, ¶¶6-7, 79; Ex. 1002, ¶103. Iwasaki thus provided strong incentive to combine. Ex. 1002, ¶103.

It would have further been obvious in view of Gambini to include a "heating element" with "openings" as required by claim 1. As discussed in Ground 1 for this claim element, such heating elements were not only well known but ubiquitous in cyclers. To boot, Gambini discloses the use of a such a heating element in a cycler to resolve the well-known problem of "sample condensation" endemic to cyclers since the advent of PCR. Ex. 1007, 7:1-7, claim 5; Ex. 1002, ¶104.

Predictable combination of known elements: The claimed devices are merely a combination of known elements with predictable results, since Iwasaki's optics head and Gambini's heated lid could be included in Pantoliano's cycler with no change in their functions, with entirely predictable results. Iwasaki's reading head performed the same function as Pantoliano's sensor, and was compact enough for easy substitution. Gambini's heated lid was designed for microtiter sample wells in cyclers, just as Pantoliano's thermal cycling block also was. Ex. 1005, 16:15-18; Ex. 1007, 6:22-23; Ex. 1002, ¶105. Thus, combining Iwasaki's optics head and Gambini's heated lid with Pantoliano's cycler was merely a matter of routine combination with entirely predictable results.

Design incentives and other market forces: Even if the applied references had lacked suggestions to combine, artisans had stong incentives to do so. Ex. 1002, ¶106. To begin with, there was immense market incentive to apply Iwasaki's optics head to thermal cyclers. Cyclers were more popular than DNA chip readers, being found in every lab and clinic as one of the most-used instruments there. Ex. 1010, 31; Ex. 1013, 17; Ex. 1012, 247; Ex. 1002, ¶106. Since optics heads like Iwasaki's had already been used to analyze fluorescent DNA in DNA chips and sample wells in other scanning devices, it was only a matter of time before such optics heads and their associated scanning mechanisms were used in cyclers as well. Ex. 1009, ¶¶75-76; Ex. 1006, 2:65-3:6; Ex. 1002, ¶106.

Artisans would also have been quick to note that Iwasaki's optics head provided exactly the features that customers wanted in cyclers. As one review noted, a "small footprint," low cost, and short amplification time were critical selling points in the "cut-throat" business of cyclers. Ex. 1014, 1-2; Ex. 1002, ¶107. Iwasaki emphasized that its optics head was "very compact and lightweight," which reduced "manufacturing costs" and allowed the overall device to be "portable" for "onsite DNA analysis in clinics and customs offices." Ex. 1009, ¶¶6-7, 79; Ex. 1002, ¶107. Another design incentive known to artisans was that Iwasaki's optics head avoided known drawbacks of optical fibers which were included in Pantoliano's sensor: detection was less reproducible because "light communication efficiency ... changed" as fibers bent during scanning, "move range [wa]s limited ... [by] bendability," and fibers were prone to breakage. Ex. 1030, 2:56-84; Ex. 1002, ¶107. It was known that "movement" of fiber optic probes like Pantoliano's slowed down head movement, produced "stresses that cause mechanical failure" and caused "variations in their optical properties," creating "inconsistencies in readings between different wells." Ex. 1031, 2:15-41; Ex. 1002, ¶107. Such design incentives would have further prompted artisans to switch to Iwasaki's optics head in Pantoliano's cycler.

There was also strong design incentive to include Gambini's heated lid in Pantoliano's cycler, as already discussed in Ground 1. Because "oil-free" cycling made possible by heated lids was much preferred, there was market incentive to use Gambini's heated lids, which had became ubiquitous in cyclers by 2001. Ex. 1013, 17, 19; Ex. 1002, ¶108.

Reasonable Expectation of Success. Artisans had a reasonable expectation of success in arriving at the apparatus of claim 1 by combining Iwasaki, Pantoliano and Gambini. All three references taught that their respective components could be successfully used for the claimed purposes. Ex. 1005, 42:57-62, 21:18-19; Ex. 1007, 6:24-7:7; Ex. 1002, ¶109. Iwasaki's optics head was sensitive enough to detect hybridization fluorescence from very small DNA spots that were 30-300 μm in size, smaller than microtiter wells in the standard 96-well format. Ex. 1009, ¶¶15-16; Ex. 1002, ¶109. Iwasaki's optics head and associated scanning assembly was small and light enough to easily be incorporated within a cycler and to scan microtiter wells (3 cm x 5 cm, 100 gm). *Id.* at 55; Ex. 1002, ¶109. Although Iwasaki performed higher-resolution (and thus slower) scanning of DNA microspots, Pantoliano used the same X-Y scanning mechanism as Iwasaki's with appropriate software enabling quicker and lower-resolution scanning of cycler wells for real-time detection. Ex. 1005, 21:3-26, 40:29-40:, Fig. 38; Ex. 1002, ¶109.

As discussed in Ground 1 for this claim element for Miller's similar optics head, Pantoliano's and Gambini's teachings also provided a reasonable expectation of success in incorporating Iwasaki's optics head along with Gambini's heating element onto Pantoliano's shuttle and support. Thus, claim 1 merely combines Iwasaki's optics head and scanning assembly with a prior-art cycler equipped with a prior-art heated lid. There was already strong incentive to make this combination, and the combination was routine with only predictable results. Ex. 1002, ¶110.

Accordingly, claim 1 would have been obvious (notwithstanding objective indicia of nonobviousness which are discussed for all claims in Section XI, below).

Independent Claim 13 (preamble) and (a). As discussed already for claim 1 (preamble) and (a) in Ground 1, artisans would have understood that the combination cycler was a "*thermal cycler apparatus comprising a thermal cycler having an exterior housing and a plurality of sample wells for holding reaction vessels*" since Pantoliano and Gambini disclose this feature.

Claim 13(b). Artisans would have understood that the combination cycler had a "*heater to prevent condensation from forming on ... the reaction vessels when ... in the sample wells*." As discussed in Ground 1 for claims 1(h) and 13(b), Gambini discloses this feature.

Claim 13(c). Artisans would have understood that the heater had "*transparent portions to permit optical communication with each of the ...wells*." As discussed in Ground 1 for claims 1(j) and 13(c), Gambini discloses this feature.

Claim 13(d). Artisans would have understood that the combination cycler had "*a support structure disposed inside the exterior housing*." As discussed in this Ground for claim 1(i), Iwasaki discloses a support structure for its scanning assembly, and as discussed in Ground 1 for claim 13(d), Pantoliano and Gambini disclose supports disposed within the exterior housing of a cycler. Artisans would have recognized through common sense that these apparatus had exterior housings to prevent ambient light from interfering with detection. Ex. 1002, ¶114.

Claim 13(d) further specifies that the support is "*on an opposite side of the heater from the ...wells*." As discussed in Ground 1 for claims 1(i) and 13(d), the incorporation of Gambini's lid heater into Pantoliano's cycler would have resulted in Pantoliano's support being "*on an opposite side of the heater from the ...wells,*" with Pantoliano's shuttle providing a mounting site for Iwasaki's optics head. Ex. 1002, ¶115. Iwasaki's scan head could alternatively be incorporated into Pantoliano's cycler by incorporating Iwasaki's shuttle and support and optics head over Pantoliano's cycling block, resulting in Iwasaki's support being "*on an opposite side of the heater from the ...wells*." Ex. 1002, ¶115.

Claim 13(e). Artisans would have understood that the combination cycler had a "*shuttle movably mounted on the support structure*" Ex. 1002, ¶116. As discussed in this Ground for claim 1(b), Iwasaki discloses this feature. As discussed in Ground 1 for claim 13(e), Pantoliano discloses this feature as well. Ex. 1002, ¶116.

Claim 13(f). Artisans would have understood that the combination cycler had a "*detection module attached to the shuttle ... including a module housing having an opening ... oriented toward the ...wells when the thermal cycler is ... operating*." As discussed in this Ground for claims 1(c) and (d), Iwasaki discloses this feature. As discussed in Ground 1 for this claim element, Pantoliano discloses this feature as well. Ex. 1002, ¶117.

Claim 13(g) and (h). Artisans would have understood that the combination cycler had an "*excitation light generator*" and an "*emission light detector*" that are both "*disposed entirely within the module housing*." As discussed in this Ground for claim 1(e) and (f), Iwasaki discloses in-head placement (Fig. 1) of both these components within the housing of the optics head. Ex. 1002, ¶118.

Claim 13(i). Artisans would have understood that the "*shuttle is movable to position the detection module in optical communication with different sample wells ... through the transparent portions of the heater*." As discussed in this Ground for Claims 1(i) and (j), Iwasaki's optics head is movable in two dimensions in order to scan separate samples in a sample array. As discussed in Ground 1 for claim 1(i) and (j), Pantoliano discloses this feature too.

The rationales for obviousness and expectation of success discussed above for claim 1 at the beginning of this Ground apply equally to claim 13. As also discussed in Ground 1 for claim 13, there was strong reason to include the additional limitations of claim 13. And Pantoliano's cycler already had an exterior housing, requiring no further effort in making the combination. Ex. 1002, ¶¶120. Thus, the additional limitations of claim 13 over those of claim 1 would have been obvious. Ex. 1002, ¶120.

Claims 2 and 20. Claims 2 and 20 recite the apparatus of claims 1 and 13 respectively, wherein an "*excitation optical path from the ... generator to the opening*" of the optics head and a "*detection optical path from the opening to the ... detector*" both have "*a fixed length*" (claim 2) or are both defined by "*a plurality of optical components*" for light of an excitation or detection wavelength, wherein "*all of the optical components ... are disposed within the housing*" of the optics head (claim 20). Base claims 1 and 13 were obvious as discussed above. Further, Iwasaki's optics head is self-contained so that all "optics, elements, and circuits ... are integrated, and ... housed inside a single case 26" as shown in Fig. 1. Ex. 1009, ¶55, Fig. 1; Ex. 1002, ¶121. Because all these components "are integrally mounted on a single board," these optical components define an optical path of fixed length as required by claim 2; and all optical components are within the head's housing (Fig. 1) as required by claim 20. *Id*. at ¶32; Ex. 1002, ¶121. The rationales for obviousness and expectation of success already discussed in this Ground for base claims 1 and 13 apply equally to claims 2 and 20, which thus were obvious. Ex. 1002, ¶121.

Claim 3. Claim 3 recites the apparatus of claim 1, further comprising "*a calibration element*" (CE) disposed so that the optics head can move "*to be positioned in optical communication with*" CE, which "*provides a known fluorescence response*." As discussed in Ground 1, claim 3 was obvious in view of

Pantoliano's and Gambini's disclosure of such calibration elements. Ex. 1002, ¶122.

Claims 6, 7 and 19. Claims 6, 7 and 19 recite the apparatus of claims 1 and 13 respectively, wherein an "*external computer*" controls the "*positioning of the detection module with respect to the wells*" (claim 6), or the "*operation of the ... generator and ... detector*" (claim 7), or both the "*movement of the shuttle and operation of the ... generator and the ... detector ... such that emission light is measured while the shuttle is in motion*" (claim 19). As discussed for these claims in Ground 1, Pantoliano's disclosure of an external computer rendered these claims obvious. Iwasaki also discloses that a "control device 9" which is an external computer in Fig. 6, "controls both motors 4, 7" for Iwasaki's shuttle. Ex. 1009, ¶75, Fig. 6; Ex. 1002, ¶123. This device also "records the fluorescence intensities … along with the XY coordinates of the reading head." *Id*. at ¶76; Ex. 1002, ¶123. Thus, claims 6, 7 and 9 were obvious. Ex. 1002, ¶123.

Claim 8. Claim 8 recites the apparatus of claim 1, wherein "*the detection module is detachably attached to the shuttle*." As discussed in Ground 1, claim 8 was obvious in view of Pantoliano's disclosure of such removable attachment. Ex. 1002, ¶124.

Claim 10 and 15. Claims 10 and 15 recite the apparatus of claims 1 and 13, further comprising "*at least two stepper motors mounted on the support structure,* *the stepper motors being operative to move the shuttle in at least two dimensions*." Base claims 1 and 13 were obvious as discussed above. Further, both the X-axis and Y-axis worm gears in Iwasaki's scanning assembly were controlled by "motors 4, 7" where the exact choice of motor type was a routine design choice as discussed in Ground 1 for claim 10 and 15. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 10 and 15, which thus were obvious. Ex. 1002, ¶125.

Claim 16. Claim 16 recites the apparatus of claim 13, further comprising "*a fitting on an exterior surface of the housing of the detection module, the fitting adapted to attach the detection module to the shuttle, wherein the fitting provides only electrical and mechanical connections*." As discussed in Ground 1, claim 16 was obvious since it merely recites a routine design choice that was well within the skill of an artisan. Ex. 1002, ¶¶82, 126.

Claim 22. Claim 22 recites the apparatus of claim 13, "*wherein the plurality of transparent portions of the heater includes a plurality of holes extending through the heater and aligned with the sample wells*." As discussed in Ground 1, claim 22 was obvious in view of Gambini's disclosure of such a plurality of holes. Ex. 1002, ¶127.

IX. Ground 4: Claims 9, 11, 14 and 17 would have been obvious over Iwasaki, Pantoliano and Gambini in view of Miller under pre-AIA §103(a)

Claims 9, 11, 14 and 17 recite the apparatus of claims 1 and 13, wherein the "*generator comprises a light-emitting diode*" (11, 17) or the optics head "*includes at least two ... detectors*" (claims 9, 14). Base claims 1 and 13 would have been obvious over Iwasaki, Pantoliano and Gambini, as discussed above. Further, as discussed in Ground 1 for these same claims, Miller discloses an optics head like Iwasaki's, which comprises a light-emitting diode and includes two detectors. Ex. 1006, 1:55-56, 1:64-67, Figs. 1-4, 7; Ex. 1002, ¶129. The reasons for obviousness and expectation of success discussed in Ground 1 for these claims also apply here. Claim 9, 11, 14 and 17 thus were obvious. Ex. 1002, ¶129.

X. Ground 5: Claim 21 would have been obvious over Iwasaki, Pantoliano and Gambini in view of Li under pre-AIA §103(a)

Claim 21 recites the apparatus of claim 13, "*wherein the detection module is positioned such that the opening is below the plurality of sample wells*." As discussed in Ground 2 for claim 21, it was obvious in view of Li to position the optics head such that "*the opening is below the plurality of sample wells*," rendering claim 21 obvious. Ex. 1040; Ex. 1002, ¶131.

XI. Objective indicia do not support patentability

To Petitioner's knowledge, the patent owner did not offer any evidence of objective indicia of non-obviousness during prosecution for any Grounds. Ex.

1002, ¶133-136. If the patent owner relies on objective indicia, Petitioner should be provided opportunity to rebut. *See* IPR2013-00368, Paper No. 8 at 13 (2013).

XII. Certification that the patent may be contested via *inter partes* review by the Petitioner and standing (37 C.F.R. § 42.104(a))

Petitioner certifies that (1) the '504 Patent is available for IPR and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '504 Patent, and this Petition is in accordance with 37 C.F.R. § 42.106(a). A Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e) are provided.

XIII. Mandatory notices (37 C.F.R. § 42.8(a)(1))

Real Party-In-Interest (§ 42.8(b)(1)) is: Thermo Fisher Scientific Inc.

Related Matters (§ 42.8(b)(2)): The '504 Patent is asserted against Petitioner in *Bio-Rad Labs., Inc. v. Thermo Fisher Scientific Inc.*, C.A. No. 16-358 (D. Del.) (RGA). Petitioner is concurrently filing another IPR petition 2017-00054 of same claims of the '504 Patent. A related App. No. 14/480,512 is pending.

Designation of Lead and Back-Up Counsel (§ 42.8(b)(3)):

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Notice of service information (37 C.F.R. § 42.8(b)(4)) and fees:

Please direct all correspondence regarding this Petition to all designated counsel at the above addresses. Petitioner consents to service by email to *all* the email addresses provided above. The required fee is paid via Deposit Acct. No. 50-3994 (Customer No. 52059). Please charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 50-3994 (Customer No. 52059).

XIV. Conclusion

The '504 Patent claims 1-3, 6-11, 13-17 and 19-22 would have been obvious, and *inter partes* review should be instituted for each.

Respectfully submitted,

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Date: October 14, 2016

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37 C.F.R. § 42.24(d) CERTIFICATION

The undersigned hereby certifies that this submission, excluding the tables of contents, certificate of word count, exhibit list, and certificate of service, contains 13,895 words, as determined using the standard word counting feature of the Microsoft Word program.

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CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 8,236,504 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123" was served in its entirety on this day, upon Patent Owner's correspondence address of record for U.S. Patent No. 8,236,504 via FEDEX®:

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