UNITED STATES INTERNATIONAL TRADE COMMISSION

Washington, D.C.

In the Matter of	
CERTAIN MICROFLUIDIC SYSTEMS AND COMPONENTS THEREOF AND PRODUCTS CONTAINING SAME	**Inv. No. 337-TA-1100**

ORDER NO. 22: ***MARKMAN* ORDER**

(October 31, 2018)

A *Markman* hearing was held in this investigation on July 25, 2018. Counsel for Complainant 10X Genomics, Inc. ("10X"), counsel for Respondent Bio-Rad Laboratories, Inc. ("Bio-Rad"), and counsel for the Office of Unfair Import Investigations ("Staff") appeared at the hearing. In advance of the hearing, 10X, Bio-Rad, and Staff filed initial and rebuttal *Markman* briefs.[1]

[1] 10X's initial and rebuttal briefs are referenced herein as "CIB" and "CRB," respectively; Bio-Rad's initial and rebuttal briefs are referenced herein as "RIB" and "RRB," respectively; Staff's initial and rebuttal briefs are referenced herein as "SIB" and "SRB," respectively.

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I. PROCEDURAL HISTORY

This investigation was instituted to determine whether there is a violation of section 337 of the Tariff Act of 1930, as amended, in the importation into the United States, the sale for importation, or the sale within the United States after importation of certain microfluidic systems and components thereof and products containing same by reason of infringement of U.S. Patent No. 9,644,204 (''the '204 patent''); U.S. Patent No. (''the '024 patent''); U.S. Patent No. 9,695,468 (''the '468 patent''); and U.S. Patent No. 9,856,530 (''the '530 patent''). Notice of Investigation at 2 (Feb. 14, 2018); 83 Fed. Reg. 7491-92 (Feb. 21, 2018). 10X asserts that Bio-Rad infringes the following claims: claims 1-4, 6-9, 17, 20, 21, 23, 25, 27, 29, 31, and 33 of the '204 patent; claims 1, 2, 5, 8, 10, 11, 13, 15-17, 19, 21, and 22 of the '024 patent; claims 1-4, 6-9, 11, 12, 21, and 22 of the '468 patent; and claims 1-6, 8-11, 14-20, and 24-30 of the '530 patent. Notice of Investigation at 2; 83 Fed. Reg. at 7492.

The parties have agreed on constructions for the following terms:

Term	Patent	Agreed-Upon Constructions
"barcode"	'204 patent, claims 3, 6, 27, 29, 31 '024 patent, claim 1 '468 patent, claim 1 '530 patent, claims 1, 4, 11, 14, 17, 24, 25, 26, 28, 29, 30	"label that may be attached to an analyte to convey identifying information about the analyte"
"wherein said capsules are [capsule is] configured to release their [its] contents into said droplets [droplet] upon the application of a stimulus"	'204 patent, claims 1, 23, 25	plain and ordinary meaning; no construction required
"applying a stimulus to said porous gel" bead to release said oligonucleotide molecules from said porous gel bead into said droplet"	'024 patent, claim 1	plain and ordinary meaning; no construction required
"wherein said barcode molecules become detached from said gel bead"	'530 patent, claims 1, 28, 29, 30	plain and ordinary meaning and above agreed-to construction for "barcode;" no construction required

CIB, App. B.

II. LEVEL OF ORDINARY SKILL IN THE ART

Bio-Rad contends that the level of ordinary skill in the art for the asserted patents is either a Ph.D. "in molecular biology, molecular genetics, chemistry, engineering, or equivalent disciplines with two years of experience or [B.S.] in such fields with five years of experience, with such experience including library preparation methods, microfluidic technology, and/or bead attachment chemistries." RIB at 5. Staff does not address the relevant level of ordinary skill in the art. Although 10X does not address the relevant level of ordinary skill in the art in its briefs, its expert does so in a declaration submitted in support of 10X's initial brief ("Butte Initial Declaration"). In that declaration, Dr. Atul J. Butte opines that a person of ordinary skill in the

art "would have a master's degree in bio-engineering, genetics, biochemistry or a related discipline, with two to three years of academic, research, or industry experience in the field of genomic sequencing solutions." Butte Initial Declaration at ¶ 22. In his declaration submitted in support of 10X's rebuttal brief ("Butte Rebuttal Declaration"), Dr. Butte states that the differences between the parties' proposed definitions of the level of ordinary skill in the art are immaterial to the claim construction disputes. Butte Rebuttal Declaration at ¶ 7.

Accordingly, for the purposes of this order, I adopt Bio-Rad's proposed definition of the level of ordinary skill.

III. LEGAL STANDARDS

"The construction of claims is simply a way of elaborating the normally terse claim language[] in order to understand and explain, but not to change, the scope of the claims." *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000) (alterations in original) (quoting *Scripps Clinic v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991)). "[O]nly those [claim] terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Claim construction focuses mainly on the intrinsic evidence, which consists of the claims themselves, the specification, and the prosecution history. *See generally Phillips v. AWH Corp.*, 415 F.3d 1303, 1313-17 (Fed. Cir. 2005) (*en banc*). The words of a claim "'are generally given their ordinary and customary meaning,'" which is "the meaning that the term would have to a person of ordinary skill in art" as of the date that the patent application was filed. *Id.* at 1312-13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)) (citations omitted). A person of ordinary skill in the art "is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire

patent, including the specification." *Id.* In some cases, "the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges." *Id.* at 1314. Often, however, "determining the ordinary and customary meaning of the claim requires examination of terms that have a particular meaning in a field of art." *Id.* "[T]he court looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.'" *Id.* (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). Those sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.*

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Id.* at 1312 (quoting *Innova*, 381 F.3d. at 1115)). "Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1314. For example, "the context in which a term is used in the asserted claim can be highly instructive," and "[o]ther claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term." *Id.*

"[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (quoting *Vitronics*, 90 F.3d at 1582). "The longstanding difficulty is the contrasting nature of the axioms that (a) a claim must be read in view of the specification and (b) a court may not read a limitation into a claim from the specification." *Innova*, 381 F.3d at 1117.

In addition to the claims and the specification, the prosecution history should be

examined if in evidence. "The prosecution history . . . consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent. Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

If the intrinsic evidence does not establish the meaning of a claim, then extrinsic evidence may be considered. Extrinsic evidence "consists of all evidence external to the patent and the prosecution history, including inventor and expert testimony, dictionaries, and learned treatises." *Id.* at 1317. Extrinsic evidence is generally viewed "as less reliable than the patent and its prosecution history in determining how to read claim terms." *Id.* at 1318. "The court may receive extrinsic evidence to educate itself about the invention and the relevant technology, but the court may not use extrinsic evidence to arrive at a claim construction that is clearly at odds with the construction mandated by the intrinsic evidence." *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 977 (Fed. Cir. 1999).

Although "[c]laim terms are generally given their plain and ordinary meanings to one of skill in the art when read in the context of the specification and prosecution history," there are two instances in which a court will depart from the plain and ordinary meaning. *Hill-Rom Service, Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014). The first is when a patentee acts as its own lexicographer. *Id.* "To act as its own lexicographer, a patentee must 'clearly set forth a definition of the disputed claim term.'" *Thorner v. Sony Comput. Entm't Am.*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) (quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366

(Fed. Cir. 2002)). The second is when the patentee disavows the full scope of the claim term. *Id.* Disavowal can be effectuated by language in the specification or the prosecution history. *See Phillips*, 415 F.3d at 1316-17. "In either case, the standard for disavowal is exacting, requiring clear and unequivocal evidence that the claimed invention includes or does not include a particular feature." *Poly-America, L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1136 (Fed. Cir. 2017).

IV. THE ASSERTED PATENTS

A. The '024 and '468 Patents

Through application 13/966,150 ("the '150 application"), which was filed on August 13, 2013, the '468 and '024 patents claim priority to six provisional applications filed between August 14, 2012 and July 10, 2013. '024 patent, cover; '468 patent, cover.[2] The '024 patent was filed as a divisional of the '150 application and the '468 patent was filed as a continuation of the '150 application. '024 patent, cover; '468 patent, cover. Because of their ancestry, the '024 and '468 patents share a common specification. The patents identify Benjamin Hindson, Serge Saxonov, and Michael Schnall-Levin as inventors. '024 patent, cover; '468 patent, cover.

1. The Specification

Analysis of biological materials, such as sequencing nucleic acids, requires proper sample preparation. '024 patent, col. 1:28-30. "Sample preparation may . . . involve fragmenting molecules, isolating molecules, and/or attaching unique identifiers to particular fragments of molecules . . . ." *Id.* at col. 1:34-37. A microwell partition capsule array can be used in sample preparation operations. *Id.*, col. 4:28-29. Such a device consists of "an assembly of partitions (*e.g.*, microwells, droplets) that are loaded with microcapsules." *Id.*, col. 4:24-27.

[2] The '024 and '468 patents are attached to 10X's initial brief as Exhibits 1 and 3, respectively.

The array divides the sample "such that a portion of the sample is present in each partition." *Id.*, col. 4:29-32. Each partition "may include one or more capsules that contain one or more reagents (*e.g.*, enzymes, unique identifiers (*e.g.*, bar codes), antibodies, *etc.*)." *Id.*, col. 4:41-44. A "trigger" can be used to cause the microcapsules to release the reagents into the partitions, so that the reagents come into contact with the subdivided sample. *Id.*, col. 4:44-48.

Microcapsules are used (1) to "provide for the controlled and/or timed release of reagents for sample preparation of an analyte," (2) to control the release and transport of reagents, (3) to deliver reagents in discrete and definable amounts, (4) to "prevent premature mixing of reagents with the sample," and (5) to ease handling of and limit contact with reagents. *Id.*, col. 6:62-col. 7:13. Microcapsules can be formed using gel beads. *Id.*, col. 9:28-35. Analytes and/or reagents can "be coupled/ immobilized to the interior surface of a gel bead (*e.g.*, the interior accessible via diffusion of an oligonucleotide barcode and/or materials used to generate an oligonucleotide barcode) and/or the outer surface of a gel bead." *Id.*, col. 9:36-42. Release of the analytes or reagents from the microcapsule may be the result of applying a trigger. *Id.*, col. 22:4-6. Various types of stimuli can be used as a trigger, including chemical stimuli, enzymes, light, heat, and magnetic fields. *Id.*, col. 19:43-48, col. 22:4-21.

One sample preparation reagent that can be delivered by a microcapsule is a "molecular barcode." *Id.*, col. 12:9-14. For most applications, such as in the case of the nucleic acid sequencing, analyzing multiple samples simultaneously "substantially decreases the cost of analysis as well as increases through-put of the process." *Id.*, col. 12:33-36. To analyze multiple samples, different samples are pooled together. *Id.*, col. 12:36-39. Before the samples are pooled together, the analytes from each sample are tagged with a unique identifier, known in the art as a "molecular barcode," so that analytes from different samples can be identified and

tracked in the pooled sample. *Id.*, col. 12:11-13, col. 12:36-39. Molecular barcodes "may comprise a variety of different forms such as oligonucleotide bar codes, antibodies or antibody fragments, fluorophores, nanoparticles, and other elements or combinations thereof." *Id.*, col. 12:14-17. In nucleic acid sequencing, oligonucleotide barcodes are particularly useful. *Id.*, col. 12:43-44.

2. Asserted Claims

10X is asserting claims 1, 2, 5, 8, 10, 11, 13, 15-17, 19, 21, and 22 of the '024 patent and claims 1-4, 6-9, 11, 12, 21, and 22 of the '468 patent.

a. The Asserted Claims of the '024 Patent

Of the asserted claims of the '024 patent, claim 1 is independent and the remaining claims depend directly or indirectly from claim 1. Claim 1 recites:

> A method for sample preparation, comprising:
>
> a) providing a droplet comprising a porous gel bead and a target nucleic acid analyte, wherein said porous gel bead comprises at least 1,000,000 oligonucleotide molecules comprising barcode sequences, wherein said oligonucleotide molecules are releasably attached to said porous gel bead, wherein said barcode sequences are the same sequence for said oligonucleotide molecules;
>
> b) applying a stimulus to said porous gel bead to release said oligonucleotide molecules from said porous gel bead into said droplet, wherein upon release from said porous gel bead, a given oligonucleotide molecule from said oligonucleotide molecules attaches to said target nucleic acid analyte; and
>
> c) subjecting said given oligonucleotide molecule attached to said target nucleic acid analyte to nucleic acid amplification to yield a barcoded target nucleic acid analyte.

Id., col. 33:56-col. 34:7.

Claims 2, 5, 8, 11, 13, 15, 16, 19, and 21 depend directly from claim 1. Claim 2 requires that the droplet be "an aqueous droplet in a continuous oil phase." *Id.*, col. 34:8-9. Claim 5 requires that the stimulus applied to the gel bead be "selected from the group consisting of a biological stimulus, a chemical stimulus, a thermal stimulus, an electrical stimulus, a magnetic stimulus, and a photo stimulus." *Id.*, col. 34:15-19. Claim 8 requires that the oligonucleotide molecule attached to the analyte have "a region which functions as a primer during said nucleic acid amplification." *Id.*, col. 34:25-28. Claim 11 requires that the "droplet further comprise[] a polymerase." *Id.*, col. 34:34-35. Claim 13 requires the nucleic acid analyte to be selected from a particular group. *Id.*, col. 34:39-47. Claim 15 requires that the oligonucleotide molecules be reversibly immobilized to the porous gel bead. *Id.*, col. 34:51-53. Claim 16 requires that the droplet "comprise[] a plurality of target nucleic acid analytes, which plurality of target nucleic acid analytes comprises said target nucleic acid analyte." *Id.*, col. 34:54-56. Claim 19 requires that the oligonucleotide molecules attach to the target nucleic acid analytes by hybridization. *Id.*, col. 34:.65-67. Claim 21 requires that the gel bead be formed from polymer gel. *Id.*, col. 35:4-5.

Claim 10 requires that the primer of claim 8 be "configured to amplify said target nucleic acid analyte" so that a barcoded target nucleic acid analyte is produced. *Id.*, col. 34:31-33. Claim 17 requires that each of the plurality of target nucleic acid analytes of claim 16 attach to one of the oligonucleotide molecules. *Id.*, col. 34:58-61. Claim 22 requires that the polymer gel of claim 21 be a polyacrylamide. *Id.*, col. 35:6-7.

b. The Asserted Claims of the '468 Patent

Of the asserted claims of the '468 patent, claim 1 is independent and the remaining claims depend directly or indirectly from claim 1. Claim 1 recites:

A method for droplet generation, comprising:

(a) providing at least 1,000,000 oligonucleotide molecules comprising barcode sequences, wherein said barcode sequences are the same sequence for said at least 1,000,000 oligonucleotide molecules, wherein said at least 1,000,000 oligonucleotide molecules are releasably attached to a bead, wherein said bead is porous;

(b) combining said at least 1,000,000 oligonucleotide molecules and a sample comprising a nucleic acid analyte each in an aqueous phase at a first junction of two or more channels of a microfluidic device to form an aqueous mixture comprising said at least 1,000,000 oligonucleotide molecules attached to said bead and said sample; and

(c) generating a droplet comprising said at least 1,000,000 oligonucleotide molecules attached to said bead and said sample comprising said nucleic acid analyte by contacting said aqueous mixture with an immiscible continuous phase at a second junction of two or more channels of said microfluidic device.

Id., col. 33:56-col. 34:9.

Claims 2, 6-9, 12, 21, and 22 depend directly from claim 1. Claim 2 requires that the aqueous fluid formed at the first junction include a reagent necessary for amplification of the nucleic acid analyte. *Id.*, col. 34:10-18. Claim 6 requires that the bead be formed from a polyacrylamide. *Id.*, col. 34:25-26. Claim 7 requires that the bead be a gel bead. *Id.*, col. 34:27. Claim 8 requires that the "at least 1,000,000 oligonucleotide molecules" include uracil. *Id.*, col. 34:28-29. Claim 9 requires that the "at least 1,000,000 oligonucleotide molecules" have a region that functions as a primer. *Id.*, col. 34:30-32. Claim 12 requires that the nucleic acid analyte be selected from a particular group. *Id.*, col. 34:37-46. Claim 21 requires that after the generation of a droplet "a given oligonucleotide molecule of said at least 1,000,000 oligonucleotide molecules attaches to said nucleic acid analyte," before being "subjected to nucleic acid amplification to yield a barcoded nucleic acid analyte." *Id.*, col. 35:3-9. Claim 22 requires the bead to have a chemical cross-linker. *Id.*, col. 35:12-13.

Claim 3 requires that the reagents of claim 2 be situated in the droplet. *Id.*, col. 34:19-20. Claim 4 requires that the reagents of claim 3 include polymerase. *Id.*, col. 34:23-24. Claim 11 requires that the primer of claim 9 be used to amplify the nucleic acid analyte. *Id.*, col. 34:35-36.

B. The '204 Patent

The '204 patent issued on May 9, 2017 from an application filed on February 7, 2014. '204 patent, cover.[3] The '204 patent claims priority to four provisional applications filed between February 8, 2013 and July 10, 2013. The provisional applications to which the '204 patent claims priority are also relied on for priority by the '024 and '468 patents. The patent names Benjamin Hindson, Serge Saxonov, Kevin Ness, Paul Hardenbol, Christopher Hindson, Donald Masquelier, Mirna Jarosz, and Michael Schnall-Levin as inventors. Three of the named inventors Benjamin Hindson, Mr. Saxonov, and Mr. Schnall-Levin—are also the named inventors of the '024 and '468 patents.

1. The Specification

The disclosed subject matter of the '204 patent is similar to that of the '024 and '468 patents. As with those patents, the '204 patent is directed to sample preparation methods and discloses "compositions comprising a plurality of capsules, the capsules situated within droplets in an emulsion, wherein the capsules are configured to release their contents into the droplets upon the application of a stimulus." *Id.*, col. 1:42-46. The capsules may contain reagents and/or analytes. *Id.*, col. 1:47-48.

[3] The '204 patent is attached to 10X's initial brief as Exhibit 5.

2. Asserted Claims

10X is asserting claims 1-4, 6-9, 17, 20, 21, 23, 25, 27, 29, 31, and 33 of the '204 patent. Claims 1, 23, and 25 are independent and the remaining claims depend directly or indirectly from these claims. Claim 1 recites:

> A composition comprising a plurality of capsules, said capsules situated within droplets in an emulsion, wherein said capsules are configured to release their contents into said droplets upon the application of a stimulus to provide said contents in said droplets in said emulsion, wherein said stimulus is selected from the group consisting of a change in pH, a change in ion concentration, reduction of disulfide bonds, and combinations thereof.

Id., col. 44:42-48.

Claims 2, 17, 20, 21, 27, and 33 depend directly from claim 1. Claim 2 requires that "at least one of [the] capsules and [the] droplets comprise a species selected from the group consisting of a reagent and an analyte." *Id.*, col. 44:50-52. Claim 17 requires that the "droplets comprise a fluid that is of a lesser density than the density of [the] capsules." *Id.*, col. 45:27-29. Claim 20 requires that the stimulus be applied to the capsules. *Id.*, col. 45:37-38. Claim 21 requires that the stimulus be applied to the droplets. *Id.*, col. 45:39-40. Claim 27 requires that the capsules' "contents comprise at least 10,000 barcoded oligonucleotides releasably attached to each of [the] capsules." *Id.*, col. 46:24-26. Claim 33 requires that the capsules be gels. *Id.*, col. 46:42-43.

Claims 3, 4, and 6-9 depend indirectly from claim 1. Claim 3 depends from claim 2 and requires that the reagent be selected from a group of reagents. *Id.*, col. 44:53-57. Claim 4 depends from claim 3 and requires that the reagent be selected from a group of enzymes. *Id.*, col. 44:58-61. Claim 6 depends from claim 3 and requires that the barcode be an oligonucleotide barcode. *Id.*, col. 44:64-65. Claim 7 depends from claim 2 and requires that the analyte be

selected from a group of analytes. *Id.*, col. 44:66-col. 45:2. Claim 8 depends from claim 7 and requires that the analyte be a polynucleotide. *Id.*, col. 45:3-4. Claim 9 depends from claim 8 and requires that the polynucleotide be selected from a group of polynucleotides. *Id.*, col. 45:5-7.

Claim 23 recites:

> A device comprising a plurality of partitions, wherein at least one partition of said plurality of partitions comprises a capsule, wherein said capsule is situated within a droplet in an emulsion, wherein said capsule is configured to release its contents into said droplet upon the application of a stimulus to provide said contents in said droplet in said emulsion, wherein said stimulus is selected from the group consisting of a change in pH, a change in ion concentration, reduction of disulfide bonds, and combinations thereof.

Id., col. 45:51-58. Claim 29 depends from claim 23 and requires that the capsules' "contents comprise at least 10,000 barcoded oligonucleotides releasably attached to each of [the] capsules." *Id.*, col. 46:30-32.

Claim 25 recites:

> A method comprising:
>
> a. providing a plurality of inner capsules, said inner capsules situated within outer capsules in an emulsion, wherein said inner capsules are configured to release their contents into said outer capsules upon the application of a stimulus, wherein said stimulus is selected from the group consisting of a change in pH, a change in ion concentration, reduction of disulfide bonds, and combinations thereof; and
>
> b. providing a stimulus to cause said inner capsules to release their contents into said outer capsules in said emulsion.

Id., col. 46:3-12. Claim 31 depends from claim 25 and requires that the capsules' "contents comprise at least 10,000 barcoded oligonucleotides releasably attached to each of [the] capsules." *Id.*, col. 46:36-38.

C. The '530 Patent

The '530 patent issued on January 2, 2018 from an application filed on May 5, 2017. '530 patent, cover.[4] Through intervening applications, the '530 patent is a continuation in part of an application filed on February 7, 2014. *Id.* The '530 patent also claims priority to five provisional applications filed between December 14, 2012 and July 10, 2013. *Id.* Four of the provisional applications to which the '204 patent claims priority are also relied on for priority by the '024, '468, and '204 patents. The patent names Benjamin Hindson, Serge Saxonov, Kevin Ness, Paul Hardenbol, Mirna Jarosz, and Michael Schnall-Levin as inventors. These same individuals are named inventors of the '203 patent and three of them—Mr. Hindson, Mr. Saxonov, and Mr. Schnall-Levin—are named inventors of the '024 and '468 patents.

1. The Specification

The claimed subject matter of the '530 patent is similar to the subject matter disclosed in the '024, '468, and '204 patents. As with those patents, the '530 patent discloses sample preparation methods that use microcapsules and beads to provide reagents and analytes in response to stimuli. '530 patent, col. 23:60-col. 24:13.

2. Asserted Claims

10X is asserting claims 1-6, 8-11, 14-20, and 24-30 of the '530 patent. Claim 1 is independent and the remaining claims depend directly or indirectly from claim 1. Claim 1 recites:

> A method for nucleic acid preparation or analysis, comprising:
>
> (a) providing:
>
> (i) at least 1,000 gel beads;

[4] The '530 patent is attached to 10X's initial brief as Exhibit 7.

(ii) releasably attached to each of said at least 1,000 gel beads, at least 1,000 barcode molecules comprising identical barcode sequences that are distinct from barcode sequences of at least 1,000 barcode molecules releasably attached to any other gel bead of said at least 1,000 gel beads; and

(iii) a plurality of cells each comprising a plurality of polynucleotide molecules;

(b) generating a plurality of droplets, wherein at least 1,000 droplets of said plurality of droplets each comprise:

(i) a single gel bead from said at least 1,000 gel beads; and

(ii) a single cell from said plurality of cells; and

(c) in each of said at least 1,000 droplets, using said plurality of polynucleotide molecules from said single cell and barcode molecules of said at least 1,000 barcode molecules from said single gel bead to generate a plurality of barcoded polynucleotide molecules,

wherein said barcode molecules become detached from said gel bead.

Id., col. 47:58-67, col. 48:57-col. 49:4.

Claims 2, 3, 5, 8-11, 14, 15, 17, 20, and 24-30 depend directly from claim 1. Claim 2 requires that the plurality of polynucleotide molecules be released in each of the at least 1,000 droplets before step (c) of claim 1. *Id.*, col. 49:7-10. Claim 3 requires that the polynucleotide molecules be messenger ribonucleic acid ("mRNA") molecules. *Id.*, col. 49:8-10. Claim 5 requires that the barcoded polynucleotide molecules be released from the droplets. *Id.*, col. 49:15-17. Claim 8 requires that the barcoded polynucleotide molecules or a "derivative thereof" be sequenced. *Id.*, col. 49:27-29. Claim 9 requires that a subset of the droplets not contain a cell. *Id.*, col. 49:30-31. Claim 10 requires that a subset of the droplets not contain a gel bead. *Id.*, col. 49:32-33. Claim 11 requires that the barcode molecules in each of the droplets be released by a single gel bead. *Id.*, col. 49:34-36. Claim 14 requires that each gel bead have at

least 1,000 barcode molecules. *Id.*, col. 49:44-45. Claim 15 requires that the gel beads recited in step (a) constitute a subset of the gel beads. *Id.*, col. 50:1-2. Claim 17 requires that the barcode molecules "comprise combinatorial assemblies of sequences from sequence modules." *Id.*, col. 50:5-7. Claim 20 requires that the plurality of droplets be at least 10,000. *Id.*, col. 50:15-16. Claim 24 requires that the gel beads contain at least 10,000 barcode molecules. *Id.*, col. 50:26-27. Claim 25 requires that the gel beads contain at least 100,000 barcode molecules. *Id.*, col. 50:28-29. Claim 26 requires that the gel beads contain at least 1,000,000 barcode molecules. *Id.*, col. 50:30-31. Claim 27 requires that the number of polynucleotide molecules range from 10,000-100,000 molecules. *Id.*, col. 50:31-32. Claim 28 requires that the barcode molecules become detached before the formation of the barcoded polynucleotide molecules. *Id.*, col. 50:35-37. Claim 29 requires that the barcode molecules become detached after the barcoded polynucleotide molecules are generated. *Id.*, col. 50:39-41. Claim 30 requires that the barcode molecules detach while the barcoded polynucleotide molecules are being generated. *Id.*, col. 50:42-44.

Claim 4 depends from claim 3 and requires that barcoded polynucleotide molecules be generated by reverse transcribing the mRNA molecules in the presence of the barcode molecules. *Id.*, col. 49:11-14. Claim 6 depends from claim 5 and requires that the barcoded polynucleotide molecules be amplified by nucleic acid amplification after the barcoded polynucleotide molecules are released from the droplets. *Id.*, col. 49:18-22. Claim 18 depends from claim 17 and requires that each of the combinatorial assemblies comprise a first sequence and a second sequence. *Id.*, col. 50:8-10. Claim 18 depends from claim 17 and requires that each of the combinatorial assemblies comprise a first sequence, a second sequence, and a third sequence. *Id.*, col. 50:11-14.

V. CLAIM CONSTRUCTION

Because the asserted patents are directed to similar subject matter, share common inventors, and stem from common priority documents, the claim construction disputes cut across patents. The disputed terms can be placed into five categories, which are addressed below.

A. "1,000,000 oligonucleotides comprising barcode sequences"

"1,000,000 oligonucleotide molecules comprising barcode sequences" ('024 patent, claim 1; '468 patent claim 1)	
Party	**Construction**
10X	Plain meaning and proposed construction for "barcode sequence"
Bio-Rad	"1,000,000 oligonucleotide molecules, part of which are barcode sequences"
Staff	"1,000,000 oligonucleotide molecules that include, but are not necessarily limited to, barcode sequences"

Claim 1 of the '024 patent and claim 1 of the '468 patent require "at least 1,000,000 oligonucleotide molecules comprising barcode sequences" that are "releasably attached" to a porous bead. '024 patent, col. 33:57-60; '468 patent, col. 33:57-63. The parties agree that the recited oligonucleotide molecules encompass molecules that have a barcode sequence and components in addition to the barcode sequence, but disagree on whether the claims encompass molecules consisting solely of a barcode sequence. Bio-Rad contends that the oligonucleotide molecules consisting solely of a barcode sequence fall outside of the scope of the claims, whereas 10X and Staff argue that the claims capture such molecules.

The plain language of the claims is consistent with 10X's and Staff's position. The plain and ordinary meaning of "comprise" is "to include esp. with a particular scope," "to be made up of," "compose," or "constitute." Webster's Ninth Collegiate Dictionary (1984) at 270-71.[5] All

[5] When used as a transitional phrase to join the preamble of a claim with the claim's body, the term "comprising" is open-ended and allows for, but does not require, additional elements. *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382 83 (Fed. Cir. 2000) ("The

of the definitions of "comprise" are consistent with 10X's and Staff's position that the claimed molecules encompass oligonucleotide molecules consisting solely of a barcode sequence. None of the definitions are consistent with Bio-Rad's position that the oligonucleotide molecule must have elements in addition to the barcode sequence.

The specification further supports 10X's and Staff's position. Describing the use of "oligonucleotide barcodes" to tag analytes, the specification describes the oligonucleotide barcodes as "compris[ing] a unique sequence (*e.g.*, a barcode sequence) that gives the oligonucleotide barcode its identifying functionality." '468 patent, col. 12:44-47. The specification notes that "an oligonucleotide barcode may consist solely of a unique barcode sequence or may be included as part of an oligonucleotide of longer sequence length." *Id.*, col. 12:58-60. Thus, the specification expressly contemplates that an oligonucleotide molecule used to tag analytes can either consist solely of a barcode sequence or include additional elements.

Bio-Rad counters that the specification supports its proposed construction. In particular, Bio-Rad points to a portion of the specification in which the term "oligonucleotide barcode" is used to refer to oligonucleotide barcodes consisting solely of a barcode sequence and the term "larger oligonucleotide" in used to refer oligonucleotide barcodes having elements in addition to the barcode sequence. *Id.*, col. 13:6-10. Bio-Rad argues that the specification's use of the term "a larger oligonucleotide comprising an oligonucleotide barcode" to describe oligonucleotide

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phrase 'consisting of' is a term of art in patent law signifying restriction and exclusion, while, in contrast, the term 'comprising' indicates an open-ended construction. . . . A drafter uses the term 'comprising' to mean 'I claim at least what follows and potentially more.'") (internal citation omitted). In the instant case, however, the term "comprising" is not being used as a transitional phrase. Accordingly, the term "should be interpreted according to the normal rules of claim interpretation." *Moleculon Research Corp. v. CBS Inc.*, 793 F.2d 1261, 1272 n. 8 (Fed. Cir. 1986), *abrogated on other grounds*, *Egyptian Goddess, Inc. v. Swisa, Inc.*, 543 F.3d 665 (Fed. Cir. 2008).

As originally drafted, application claim 78, which would mature into claim 1, was directed to a method of sample preparation wherein an "oligonucleotide barcode" and an analyte are released from a microcapsule in response to a stimulus. '024 Patent File History, Amendment (Feb. 17, 2017) at 3.[6] The examiner rejected application claim 78 as anticipated and obvious in view of several prior art references. *See, generally*, '024 Patent File History, Office Action (June 24, 2016). The applicants filed two responses to the office action. In the first response, the applicants extensively amended application claim 78. '024 Patent File History, Response (Dec. 21, 2016) at 2. As amended, the application claim required a "droplet comprising a porous gel bead and a target nucleic acid analyte, wherein said porous gel bead comprises at least 1,000,000 oligonucleotide barcodes" and required the barcoded analyte to undergo an amplification step. *Id.*

The applicants argued that the amended application claim was allowable over the cited prior art, because the prior art did not disclose one or more of the following elements: (1) "providing a droplet comprising a porous gel bead . . . wherein said porous gel bead comprises at least 1,000,000 oligonucleotide barcodes that are releasably attached to said porous gel bead," (2) "applying a stimulus to said porous gel bead to release said oligonucleotide barcodes from said porous gel bead, wherein upon release from said gel bead, a given oligonucleotide barcode from said oligonucleotide from said oligonucleotide barcodes attaches to said target nucleic acid analyte," and (3) "subjecting said given oligonucleotide barcode attached to said target nucleic acid analyte to nucleic acid amplification to yield a barcoded target nucleic acid analyte." *Id.* at 8-14. Notably, none of the bases cited by the applicants to distinguish the pending claims from the prior art relate to the composition of the "barcode molecules."

[6] A certified copy of the file history of the '024 patent was filed as Appendix B to the complaint.

Three months after submitting their initial response, the applicants submitted a supplementary response, amending the application claim 78 to replace the term "oligonucleotide barcodes" with the term "oligonucleotides comprising barcode sequences." '024 Patent File History, Response (Mar. 28, 2016) at 3. Bio-Rad argues that the applicants made this amendment in order to further distinguish the pending claims from the cited prior art. The prosecution history clearly indicates, however, that the amendment in the supplementary response was not made in order to distinguish prior art.

The supplementary response was filed after the examiner conducted an interview with the applicants. '024 Prosecution History, Examiner Initiated Interview Summary (Apr. 25, 2017). In that interview, the examiner informed the applicants that application claim 78 would be allowable if it was further amended "to specify that the barcode sequence of oligonucleotides are the same," not to overcome an obviousness or anticipation rejection, but to overcome a "potential rejection under 35 USC 112 second paragraph." '024 Prosecution History, Examiner Initiated Interview Summary (Apr. 25, 2017). The supplementary response was submitted eight days after the interview. Thus, amending the claims to recite "oligonucleotides comprising barcode sequences" rather than "oligonucleotide barcodes" was made "to specify that the barcode sequence of oligonucleotides are the same," not to disclaim oligonucleotide molecules that consist solely of a barcode sequence. *See Core Licensing S.A.R.L. v. LG Electronics, Inc.*, 880 F.3d 1356, 1367 (Fed. Cir. 2018) ("The patentee's statements during prosecution do not amount to a clear and unmistakable disclaimer restricting the meaning of 'un-launched state' only to those applications that are not running any processes.").

In view of the foregoing, I reject Bio-Rad's argument that the oligonucleotide molecules do not encompass molecules that consist solely of a barcode sequence. I find that the term

"1,000,000 oligonucleotides comprising barcode sequences" means "1,000,000 oligonucleotide molecules that include, but are not necessarily limited to, barcode sequences."

B. "releasably attached"

"releasably attached" ('024 patent, claim 1; '468 patent, claim 1)	
Party	**Construction**
10X	"attached, directly or through chemical moieties or chemical linkers, and releasable upon application of a stimulus"
Bio-Rad	"**wherein said oligonucleotide molecules are releasably attached to said porous gel bead "wherein said porous gel bead is configured to release said oligonucleotide molecules"** ('024 patent, claim 1) means "wherein said porous gel bead is configured to release said oligonucleotide molecules" "**wherein said at least 1,000,000 oligonucleotide molecules are releasably attached to a bead**" ('468 patent, claim 1) means "wherein said bead is configured to release said at least 1,000,000 oligonucleotide molecules" "**10,000 barcoded oligonucleotides releasably attached to [each of said capsules] [said capsule] [each of said capsule]**" ('204 patent, claim 27, 29, 31) means "10,000 barcoded oligonucleotides attached to [each of said capsules] [said capsule] [each of said capsule], which is [are] configured to release them" "**1,000 barcode molecules releasably attached to any other gel bead**" ('530 patent, claim 1) means "any other gel bead is configured to release said at least 1,000 barcode molecules" "**releasably attached to each of said at least 1,000 gel beads, at least 1,000 barcode molecules**" ('530 patent, claim 1) means "said at least 1,000 gel beads are configured to release said at least 1,000 barcode molecules"
Staff	Same as 10X's

The asserted claims of the '024, '468, and '530 patents require a gel bead comprising barcode molecules, wherein the barcode molecules are "releasably attached" to the gel bead. '024 patent, col. 33:60-62 (claim 1); '468 patent, col. 33:60-63 (claim 1); '530 patent, col. 47:62-67 (claim 1). The asserted claims of the '204 patent require a "capsule," the contents of which include barcode molecules that are "releasably attached" to the capsule. '204 patent, col. 44:42-49 (claim 1), col. 46:25-27 (claim 27), col. 46:30-32 (claim 29), col. 46:36-38 (claim 31). The asserted claims of the '024 patent require that the barcode molecules be released from the gel

bead in response to a stimulus applied to the gel bead. '024 patent, col. 33:65-col.34:1 (claim 1). The asserted claims of the '530 patent require the barcodes to "become detached" or be "released" from a gel bead without specifying how they become detached or released. '530 patent, col. 49:3-4 (claim 1) ("become detached"), col. 49:34-36 (claim 11) ("released"), col. 50:35-38 (claim 28) ("become detached"), col. 50:38-41 (claim 29) ("become detached"), col. 50:42-44 (claim 30) ("become detached"). The asserted claims of the '468 patent do not require the barcode molecules to become detached or released from the bead. '468 patent, col. 33:57-col. 34:9 (claim 1). The parties agree that the term "releasably attached" should be construed consistently across the patents. RRB at 2; CIB at 25; SIB at 30.

According to Bio-Rad, the term "releasably attached" requires that the bead or capsule be configured or designed to release the barcode molecules. RIB at 12. 10X and Staff counter that the term only requires that the barcode molecules be attached and releasable upon application of a stimulus. SIB at 16; CIB at 12-13. The term "releasably attached" is not a term of art and its meaning is apparent to even a lay judge: the barcode molecules are attached to the bead or capsule in a way that allows them be released. *Phillips*, 415 F.3d at 1314 ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words."). There is no support in the claim language, the specifications, and prosecution histories of the asserted patents for Bio Rad's proposed construction. 10X's and Staff's proposed construction is also flawed because it imports limitations from the specification into the claims.

1. Bio-Rad's proposed construction is inconsistent with the claim language of the asserted claims.

Although Bio-Rad argues that the language of the asserted claims supports its proposed construction of "releasably attached," the claim language is actually inconsistent with Bio-Rad's proposed claim construction. Bio-Rad places particular emphasis on the claim language of the '204 and '024 patents. RRB at 2-4. Independent claim 1 of the '204 patent is directed to "capsules" that "are configured to release their contents . . . upon the application of a stimulus." '204 patent, col. 44:42-49 (claim 1). Dependent claims 27, 29, and 31 require that each capsule's contents include barcode molecules "releasably attached" to the capsule. *Id.*, col. 46:25-27 (claim 27), col. 46:30-32 (claim 29), col. 46:36-38 (claim 31). The asserted claims of the '024 patents require the barcode molecules to be released in response to a stimulus applied to the gel bead. '024 patent, col. 33:65-col.34:1 (claim 1). To the extent that the claims of the '204 and '024 patents may be interpreted to require a capsule or bead configured to release the barcode molecules, such an interpretation—as acknowledged by Bio-Rad—would be based on claim language other than "releasably attached:"[7]

> **Claim 1.** A composition comprising a plurality of capsules, said capsules situated within droplets in an emulsion, wherein said ***capsules are configured to release their contents*** into said droplets upon the application of a stimulus . . . .

RRB at 3 (quoting '204 Patent, col. 44:42-49 (claim 1)) (emphasis added by Bio-Rad).

> (b) applying a ***stimulus to said porous gel bead to release said oligonucleotide molecules from said porous gel bead*** into said droplet . . . .

[7] This order is limited to addressing whether the term "releasably attached" requires a capsule or bead configured to release the barcode molecules and makes no finding on whether other claim language so requires.

Id. at 4 (quoting '024 patent, col. 33:65-col.34:1 (claim 1)) (emphasis added by Bio-Rad).

The claim language relied on by Bio-Rad with respect to the '204 and '024 patents is not present in the asserted claims of the '468 and '530 patents. Bio-Rad does not even make the argument that the claim language of the '468 patent supports its proposed construction. While requiring barcode molecules that are "releasably attached" to a gel bead, the asserted claims of the '468 patent do not require the barcode molecules to be released from the gel bead, much less be released in response to a stimulus applied to the gel bead. '468 patent, col. 33:57-col. 34:9 (claim 1). Although Bio-Rad argues that the claims of the '530 patent support its proposed construction of "releasably attached," its argument is unpersuasive. RRB at 5-6.

Independent claim 1 of the '530 patent requires barcode molecules that are "releasably attached" to the gel bead to "become detached," while certain dependent claims (*e.g.*, claim 11) require the barcode molecules to be "released." *Compare* '530 patent, col. 49:3-4 (claim 1) ("become detached") *with id*, col. 49:34-36 (claim 11) ("released"). According to Bio-Rad, "[l]ogically, 'released' must be narrower than 'detached' or Claim 11 would not be limiting Claim 1 in any way." RRB at 5 (citing *Hutchins v. Zoll Medical Corp.*, 492 F.3d 1377, 1382 (Fed. Cir. 2007). Whether "released" has a narrower scope than "detached" is irrelevant to the construction of "releasably attached." Claim 1 describes the "releasably attached" barcode molecules as "becom[ing] detached," not being "released." '530 patent, col. 47:62-66, col. 49:3-4. Accordingly, "releasably attached" barcode molecules encompasses barcode molecules that can be "detached."

2. The specifications of the asserted patents are inconsistent with Bio-Rad's proposed construction.

Bio-Rad's proposed construction is also inconsistent with the specifications of the asserted patents. The specification of the '024 and '468 patents teaches that "oligonucleotide

barcodes . . . may be coupled/immobilized to the interior surface of a gel bead (*e.g.*, the interior accessible via diffusion of an oligonucleotide barcode and/or materials used to generate an oligonucleotide barcode) and/or the outer surface of a gel bead or any other microcapsule." '024 patent, col. 9:36-42. The "[c]oupling/immobilization may be via any form of chemical bonding (e.g., covalent bond, ionic bond) or physical phenomena (*e.g.*, Van der Waals forces, dipole-dipole interactions, *etc.*)" and in certain circumstances may be reversible. *Id.*, col. 9:42-49. Bio-Rad argues that this description is inapplicable because it addresses barcode molecules that are "reversibly immobilized" on a bead or capsule, not barcode molecules that are "releasably attached" to a bead or capsule. RRB at 12-13. Bio-Rad's argument ignores that reversible immobilization is a species of releasable attachment.

The relationship between the claim term "releasably attached" and the specifications' discussion of reversible immobilization is confirmed by the '468 patent's prosecution history.[8] During the prosecution of that patent, the examiner questioned whether application "claim 99 requiring the limitation of 'said at least 1,000,000 oligonucleotide molecules are attached to said bead via a covalent bond' . . . further limit[ed] the limitation of amended claim 78, requiring 'oligonucleotide molecules [that] are releasably attached to a bead.'" '468 Patent Prosecution History, Email from B. Narayan to A. Alemozafar (Apr. 20, 2017). In response, the applicants argued that "the 'oligonucleotide molecule' of Claim 78 may be 'releasably attached to a bead' via covalent bonds or ionic bonds, to provide a few examples." '468 Patent Prosecution History, Email from A. Alemozafar to B. Narayan (Apr. 20, 2017). In support of their position, the applicants pointed to the specification's discussion of reversible immobilization and quoted the following sentences:

[8] A certified copy of the file history of the '468 patent was filed as Appendix C to the complaint.

> Coupling/immobilization may be via any form of chemical bonding (e.g., covalent bond, ionic bond) or physical phenomena (e.g., Van der Waals forces, dipole-dipole interactions, etc.). In some cases, coupling/immobilization of a reagent to a gel bead or any other microcapsule described herein may be reversible, such as, for example, via a labile moiety (e.g., via a chemical cross-linker, including chemical cross-linkers described herein). Upon application of a stimulus, the labile moiety may be cleaved and the immobilized reagent set free.

Id. (quoting '024 patent, col. 9:42-52) (internal citations omitted). The examiner agreed that the cited paragraph described how barcode molecules can be "releasably attached" using covalent bonds and ionic bonds, and allowed application claim 99. Notice of Allowability (Apr. 28, 2017) at 2-3 ("[A]n agreement was reached that the limitation of claim 99 still further limits the limitations of claim 78 because 'oligonucleotide molecules' of claim 78 may be 'releasably attached to a bead' via covalent bonds or ionic bonds, as discussed in the instant published specification paragraph 0056.").[9]

Bio-Rad further argues the specifications of the asserted patents support its proposed construction because they "describe the bead or capsule as configured to release the oligonucleotide molecules." RIB at 12-13. The patents, however, also disclose embodiments in which the barcode molecules are released by severing a portion of the barcode molecule. The '024 patent specifically discusses the use of "a labile moiety" to "coupl[e]/immobiliz[e]" a barcode molecule to a gel bead. '024 patent, col 9:45-49. In order to free the immobilized barcode, the labile moiety is cleaved "upon application of a stimulus." *Id.*, col. 9:49-51.

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[9] Both the applicants in their email to the examiner and the examiner in the interview summary refer to paragraph 56 of the application of the '024 patent. Although the "reversible immobilization" discussion occurs in paragraph 54, not paragraph 56, it is clear from the sentences quoted in the applicants' email that the applicants and examiner are referring to paragraph 54.

Importantly, the specification teaches that the labile moiety may be part of the barcode molecule itself. *Id.*, col. 9:56-59.

The specification of the '024 and '468 patents further undercuts Bio-Rad's proposed construction. The specification explains that the release of the barcode molecule can be effectuated by "[v]arious different stimuli." *Id.*, col. 19:36-38. Such a stimulus can trigger the release of barcode molecules by causing "disruption or degradation of any chemical bonds that immobilize a reagent to the microcapsule," as opposed to causing "disruption or degradation of the shell or membrane enveloping the microcapsule" or "disruption or degradation of the interior of a microcapsule." *Id.*, col. 19:39-43. This description does not limit the "chemical bonds that immobilize a reagent to the microcapsule" to chemical bonds on the bead or capsule, but encompasses chemical bonds that are part of the barcode molecules.

Despite the clarity of the specification's description, Bio-Rad argues that this portion of the specification supports its construction because

> The phrase "any chemical bonds" only concerns bonds that can be broken when a stimulus is applied to the microcapsule. It is not stating that "any chemical bonds" disrupted in any manner is within the scope of release.

RRB at 13. In the description at issue, however, the specification does not state that the "stimulus is applied to the microcapsule." *Id.* Bio-Rad's only apparent support for so interpreting the specification is the specification's statement that stimuli can be used to "'trigger release of reagents ***from the microcapsules***.'" RRB at 13 (quoting '024 patent, col. 19:36-43) (emphasis added by Bio-Rad). That a stimulus causes the barcode molecules to be released "from the microcapsules" does not necessarily mean that the stimulus acts upon the microcapsules.

3. The prosecution history of the '024 patent is inconsistent with Bio-Rad's proposed construction.

The prosecution history of the '024 patent further undercuts Bio-Rad's proposed construction. During prosecution, the examiner rejected application claims 102 and 103 as being anticipated by U.S. Patent Application 2012/0316074 ("'074 application"). '024 Patent Prosecution History, Office Action (June 24, 2016) at 4-5. Application claims 102 and 103 depended from application claim 78, which required a "microcapsule [that] is degradable upon the application of a stimulus to said microcapsule," so that an oligonucleotide barcode is released upon the application of the "stimulus to said microcapsule." '024 Patent Prosecution History, Preliminary Amendment (February 17, 2015) at 3. Application claim 103 further required the oligonucleotide barcode to be "reversibly immobilized" to the microcapsule. *Id.* at 5. The examiner found that the "reversible immobilization" limitation was satisfied by the '074 application's disclosure of an "oligonucleotide barcode . . . , which can be cut and ligated." '024 Patent Prosecution History, Office Action (June 24, 2016) at 5. In their response to the office action, the applicants did not dispute the examiner's determination that the '074 application disclosed the "reversibly immobilized" limitation. '024 Patent File History, Response (Dec. 12, 2016) at 9-10. Thus, both the examiner and the applicants understood that "reversible immobilization"—a form of releasable attachment—encompasses situations wherein a barcode molecule is released from a bead by severing a portion of the barcode molecule.

4. 10X's and Staff's proposed construction imports limitations from the specification.

10X and Staff argue that "releasably attached" should be construed to mean "attached, directly or through chemical moieties or chemical linkers, and releasable upon application of a stimulus." This proposed construction imports limitations from the specification by requiring the barcode molecule to be releasable "upon application of a stimulus" and requiring any indirect

attachment be "through chemical moieties or chemical linkers." In support of these limitations, 10X and Staff point to the specifications of the asserted patents, not the claim language. It is axiomatic that limitations from the specification should not be imported into the claims. *Phillips*, 415 F.3d at 1319-20.

Based on the foregoing, I find that "releasably attached" means "attached in a manner that allows the attached object to be released."

C. "reversibly immobilized"

"reversibly immobilized" ('024 patent, claim 15)	
Party	**Construction**
10X	"bound by a chemical bond or physical phenomenon that can be undone"
Bio-Rad	"**reversibly immobilized to said porous gel bead**" means "releasable by reversing the process of attachment to said porous gel bead"
Staff	"immobilized through any form of chemical bonding or physical phenomena that can be specifically disrupted or degraded"

Claim 15 of the '024 patent requires the barcode molecules of claim 1 to be "reversibly immobilized" to the gel bead. '024 patent, col. 34:51-53. As noted by Staff, "it is unclear what—if any—substantive dispute exists among the parties." RRB at 7. Although 10X argued at the hearing that there is some potential ambiguity that could arise from Bio-Rad's proposed construction, the cause of 10X's concern is not Bio-Rad's proposed construction of "reversibly immobilized," but Bio-Rad's proposed construction of "releasably attached." Tr. at 45 (". . . Bio-Rad's construction leaves ambiguity as to what they think it means to have the 'bead releasing the barcode.'").

Because there is no dispute regarding the interpretation of the term "reversibly immobilized," its construction is not addressed in this order. U.S. *Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims.").

D. Amplification terms

"amplification"('024 patent, claims 1, 8; '468 patent, claims 2, 21)/"amplify" ('024 patent, claim 10)/"amplifying" ('468 patent, claim 11; '530 patent, claim 6)	
Party	**Construction**
10X	***"amplification"***: "polymerization of" ***"amplify"***: "polymerize" ***"amplifying"***: "polymerizing one or more additional nucleic acid sequences based on a template nucleic acid sequence"
Bio-Rad	***"amplification"***: "creation of multiple copies of" ***"amplify"***: "create multiple copies of" ***"amplifying"***: "creating multiple copies of"
Staff	***"amplification"***: "replication" ***"amplify"***: "replicate" ***"amplifying"***: "replicating"

The asserted claims of the '024 patent require that the barcode molecule attached to a nucleic acid analyte be subjected "to nucleic acid amplification to yield a barcoded target nucleic acid analyte." '024 patent, col. 34:4-7 (claim 1). Claim 6 of the '530 patent requires a step of "amplifying" barcoded polynucleotide molecules "by nucleic acid amplification." '530 patent, col. 34:25-28. Claim 2 of the '468 patent requires forming an aqueous solution by combining the nucleic acid analyte and gel bead of claim 1 with "one or more reagents necessary for amplification." '468 patent, col. 34:10-18. Claim 11 of the '468 patent requires "amplifying" a nucleic acid analyte. *Id.*, col. 34:35-36. The parties raise two disputes concerning the construction of "amplification" and its variants. The first issue is whether amplification encompasses synthesizing complementary copies of mRNA strands through reverse transcription. The second issue is whether amplification requires the creation of multiple copies of the nucleic acid being amplified. With regard to the asserted claims of the '024 patent, the parties raise a third dispute regarding whether the amplification step must be performed within a droplet.

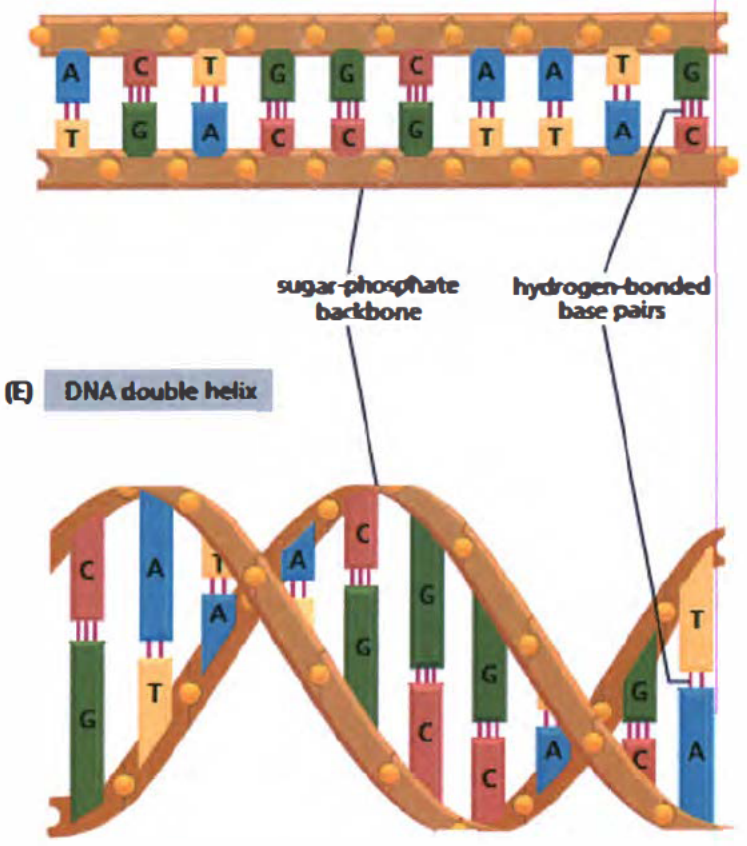
1. Amplification encompasses reverse transcription.

10X's proposed constructions of the "amplification" terms encompass reverse transcription of RNA (ribonucleic acid) into DNA (deoxyribonucleic acid). Both Bio-Rad and Staff argue that reverse transcription is not a form of amplification. For the reasons set forth below, I find that reverse transcription can be used as a method of amplification.

a. Nucleic Acid Replication and Reverse Transcription

By way of background, DNA and RNA are comprised of sequences of nucleotides. Butte Initial Declaration at ¶ 37. DNA strands are comprised of four nucleotides: adenine (A), guanine (G), cytosine (C), and thymine (T). *Id.* RNA strands are also composed of four nucleotides. With the exception of thymine, the nucleotides in an RNA strand are the same as those in a DNA strand. *Id.* Instead of thymine, RNA strands have the nucleotide uracil (U). *Id.*

DNA molecules typically occur as double-stranded molecules, known as DNA double helices. *Id.* at ¶ 39. A DNA double helix is comprised of two DNA strands oriented antiparallel to each other. *Id.* The nucleotides in one strand of a double helix are complementary to those in the other strand and bonds will form between the complementary nucleotides. *Id.* Adenine pairs with thymine and cytosine pairs with guanine. *Id.*



Alberts, Molecular Biology of the Cell (5th Ed.) ("Alberts"), Fig. 1-2 (excerpt); Butte Initial Declaration at ¶ 39.[10] In DNA replication, an enzyme called DNA polymerase binds to each strand and forms a new strand that is complementary to the template strand. Butte Initial Declaration at ¶ 40.

In a process called "transcription," a DNA strand serves as a template to create a strand of messenger RNA ("mRNA"). *Id.* at ¶ 41. In this process, an enzyme called RNA polymerase uses one DNA strand as a template to form an mRNA strand that is composed of nucleotides complementary to those on the DNA strand. *Id.* To form the mRNA strand, adenine, thymine, cytosine and guanine in the DNA strand are transcribed into uracil, adenine, guanine, and

[10] Excerpts from Alberts are attached as Exhibit 13 to 10X's initial brief and as Exhibit SMX-0010 to Staff's rebuttal brief.

cytosine, respectively. *Id.* The mRNA strand is then used to create proteins in a process known as "translation." *Id.*

Because of the complementary relationship between the nucleotide sequences comprising the DNA strand and the mRNA strand, in a process called "reverse transcription," the mRNA strand can be used as a template to form a strand of complementary DNA ("cDNA"). *Id.* at ¶ 42. To form a cDNA strand, adenine, uracil, cytosine and guanine in the mRNA strand are reverse transcribed into thymine, adenine, guanine, and cytosine, respectively. *Id.*

b. Amplification is increasing the copy number of the target sequence to be detected.

The '530 patent teaches that "[a]mplification may be used to increase the quantity of a target polynucleotide." '530 patent, col. 19:5-6. To provide a general description of "polynucleotide amplification," the '530 patent cites Application No. PCT/US 99/01705 ("'705 application").[11] '530 patent, col. 18:28-34 (teaching that "target polynucleotides" can be obtained through a variety of ways including "polynucleotide amplification (as generally described in PCT/US/99/01705)"). In addition, the '530 patent expressly incorporates the '705 application by reference. *Id.* col. 5:5-22 ("All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.").

The '705 application teaches that "[t]arget amplification involves the amplification (replication) of the target sequence to be detected, such that the number of copies of the target sequence is increased." '705 application, p. 20; *see also id.* at 2 ("Target amplification involves

[11] The '705 application is attached as Exhibit SMX-0004 to Staff's initial brief.

the amplification (*i.e.* replication) of the target sequence to be detected, resulting in a significant increase in the number of target molecules."). Accordingly, "amplification" as used in the '530 patent is a process that "increases the number of copies of the target sequence to be detected." '705 application, p. 20; *see also* '530 patent, col. 19:5-6 ("Amplification may be used to increase the quantity of a target polynucleotide.").

With regard to the '024 and '468 patents, there is no indication that "amplification" is being used differently in these patents. The '024, '468, and '530 patents share common inventors and stem from common priority documents; accordingly the term "amplification" and its variants should be construed consistently across the patents. *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005), *abrogated on other grounds as recognized in IRIS Corp. v. Japan Air lines Corp.*, 769 F.3d 1359, 1361 n. 1 (Fed. Cir. 2014) ("Because NTP's patents all derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.").

Based on the foregoing, I find that the amplification terms recited in the claims of the '530, '024 and '468 patents refers to increasing "the number of copies of the target sequence to be detected."

c. The "target sequence to be detected" includes complementary copies.

Pointing to the '705 application's equation of "amplification" to "replication," Staff argues that "amplification" requires the creation of exact copies—not complementary copies—of the target sequence. In support of this argument, Staff points to technical dictionaries defining "replication" as "the process of duplicating or reproducing, as replication of an exact copy of a polynucleotide strand of DNA or RNA." *Miller-Keane Encyclopedia and Dictionary of Medicine*, Nursing, Allied Health at 1530 (7th Ed. 2003) ("*Miller-Keane*"); *see also Oxford Dictionary of Biochemistry and Molecular Biology* at 565 (Oxford Univ. Press 1997) ("*Oxford*

Dictionary").[12] 10X, however, cites references that show that "replication" can be used more broadly to refer to the creation of complementary copies through reverse transcription. V. Potapov, *et al.*, *Base Modifications Affecting RNA Polymerase and Reverse Transcriptase Fidelity*, Nucleic Acids Research, Vol. 46, Iss. 11, June 20, 2018 ("Potapov"), at 5753, 5756 ("RNA is replicated by a reverse transcriptase to produce cDNA, then the first strand is replicated by the same reverse transcriptase to produce double-stranded DNA, which is then prepared for sequencing by ligating SMRTbell adaptors."); U.S. Patent No. 7,153,672 ("'672 patent") at 2:18-20 ("Eukaryotic genomes in particular are filled with mobile elements, retrotransposons, that use reverse transcriptase for replication.").[13]

Consistent with the references cited by 10X, the '705 application uses "amplification" (and, by extension, "replication") broadly to encompass the creation of complementary copies, as well as exact copies, of a target sequence to be detected. In particular, the '705 application discusses "strand displacement amplification" ("SDA"), as one method of target amplification. '705 application at 20-21. In SDA, a "single stranded target nucleic acid, usually a DNA target sequence, is contacted with an SDA primer." *Id.* at 20. The SDA primer hybridizes with the target sequence and is extended by an SDA polymerase to form a "newly synthesized strand." *Id.* at 20-21. The newly synthesized strand is complementary to the original strand. *Id.* at 21-22. The '705 application considers the formation of the complementary strand to be an amplification reaction noting that a "second amplification reaction can be done using the complementary target

[12] Excerpts from *Miller-Keane* and *Oxford Dictionary* are attached as Exhibits SMX-0006 and SMX-0005, respectively, to Staff's initial brief.

[13] Popatov and the '627 patent are attached as Exhibits 16 and 17, respectively, to 10X's initial brief.

sequence, resulting in a substantial increase in amplification during a set period of time." *Id.* at 22.

d. Reverse transcription can be used increase the copy number of the target sequence to be detected.

In support of its construction of "amplification," Bio-Rad places significant emphasis on the fact that reverse transcription produces a cDNA copy, not an RNA copy, of an mRNA strand. RIB at 17 ("mRNA and cDNA are not the same molecule."); Tr. at 82:13-84:12. If the cDNA copy is the "target sequence to be detected," however, reverse transcription increases the copy number of target molecules to be detected and is therefore an amplification reaction. This is shown in the '705 application's discussion of nucleic acid sequence based amplification ("NASBA"), which the '705 application teaches can be used for target amplification. '705 application at 2. In NASBA, "[a] single stranded target nucleic acid, usually an RNA target sequence," is used as a first template. *Id.* at 23. A cDNA copy of the first template is synthesized through reverse transcription. *Id.* This cDNA copy is the second template. *Id.* A strand of DNA complementary to the second template is synthesized resulting in a double-stranded cDNA copy. *Id.* at 23-24. The double-stranded copy is referred to as the third template. *Id.* Each strand of the third template is used to generate multiple RNA strands that are "essentially the same as the first template." *Id.* at 24. The method can be repeated using the newly synthesized RNA strands as the first template for the new cycle. *Id.*; *see also* U.S. Patent No. 5,409,818 ("'818 patent"), col. 5:54-56 ("Each newly synthesized first template can be converted to further copies of the second template and the third template by repeating the cycle.").[14]

[14] The '705 application incorporates by reference the '818 patent in its entirety and cites it as providing a general description of NASBA. '705 application at p. 22.

Although the RNA sequence that serves as the first template is described as an "RNA target sequence," it is not the "target sequence to be detected." In a NASBA reaction, the target sequence to be detected is typically the cDNA copy of the RNA. As the '705 application notes, it "will be appreciated by those in the art, [that] it is preferable to detect DNA strands during NASBA since the presence of the ribonuclease makes the RNA strands potentially labile." '705 application at p. 24. In the NASBA process, a substantial portion of the cDNA copies are produced through reverse transcription reactions. *Id.* ("[NASBA] result[s] in a single starting RNA template generating a single DNA duplex; however, since this DNA duplex results in the creation of multiple RNA strands, which can then be used to initiate the reaction again, amplification proceeds rapidly."). Accordingly, if the cDNA sequence is the target sequence to be detected, reverse transcription is an amplification reaction because it increases the copy number of cDNA strands. On the other hand, if the RNA sequence is the target sequence to be detected, reverse transcription would not be an amplification reaction because it does not increase the copy number of RNA strands.

Staff and Bio-Rad argue that the asserted patents distinguish amplification from reverse transcription. In particular, they point out that in identifying examples of various reactions that can be used to amplify polynucleotide analytes, the asserted patents omit reverse transcription. '204 patent, col. 31:29-40 ("An [*sic*] suitable amplification method may be utilized, including polymerase chain reaction ('PCR'), ligase chain reaction ('LCR'), helicase-dependent amplification, linear after the exponential PCR ('LATE-PCR') asymmetric amplification, digital PCR, degenerate oligonucleotide primer PCR ('DOP-PCR'), primer extension pre-amplification PCR ('PEP-PCR') and ligation mediated PCR, rolling circle amplification, multiple displacement amplification ('MDA'), and single primer isothermal linear amplification."); '530

patent, col. 18:40-43 ("Amplification may include PCR amplification, multiple displacement amplification (MDA), rolling circle amplification and other amplification methods."); '024 patent, col. 25:24-28 ("amplification reactions (e.g., PCR, qPCR, reverse-transcriptase PCR, digital PCR, etc.)"). The lists of amplification reactions provided in the patents are non-exhaustive, as indicated by the use of the words "including," "may include," "other amplification methods," "*e.g.*," and "*etc.*" Accordingly, the omission of "reverse transcription" from the list of exemplary amplification reactions is not a basis for finding that reverse for transcription cannot be used for amplification. *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1287 (Fed. Cir. 2010) ("[T]he five deposited strains and listed sequences are 'representative of' a 'type of porcine circovirus,' and thus do not constitute the entire scope of the invention.").

Bio-Rad makes two additional arguments in support of its position that the patents distinguish between amplification and reverse transcription. First, Bio-Rad argues that the '530 patent discusses reverse transcription and amplification as separate and distinct processes. Specifically, the second full paragraph of column 18 of the '530 patent discusses various amplification methods that can be used to isolate genomic DNA, before discussing the use of reverse transcription to create cDNA copies of mRNA. *Compare* '530 patent, col. 18:39-43 (discussing various methods of amplification) *with id.*, col. 18:51-54 (discussing reverse transcription). There is no inconsistency between the '530 patent's separate discussions of reverse transcription and amplification in column 18 and finding that reverse transcription can be used for amplification. In column 18, the '530 patent is not discussing amplification in general but amplification of genomic DNA. *Id.*, col. 18:37-43 ("For example, genomic DNA may be isolated with or without amplification. Amplification may include PCR amplification, multiple displacement amplification (MDA), rolling circle amplification and other amplification

methods."). Reverse transcription cannot be used to increase the number of genomic DNA copies, but—as acknowledged in the same paragraph—is used to increase the number of cDNA copies. *Id.*, 18:51-54 ("If the isolated polynucleotide is an mRNA, it may be reverse transcribed into cDNA . . . ."). Thus, the '530 patent's separate treatment of reverse transcription and amplification of genomic DNA does not indicate that reverse transcription cannot be used for amplification of cDNA strands.

Second, Bio-Rad argues that the '530 patent claims reverse transcription and amplification separately. Specifically, claim 4 depends from claim 1 through claim 3 and requires the generation of barcoded polynucleotide molecules using reverse transcription. '530 patent, col. 49:11-14. Claim 7 depends directly from claim 1 and requires the barcoded polynucleotide molecules generated in step (c) of claim 1 to be amplified. *Id.*, col. 49:23-26. Claims 4 and 7 are sister claims that depend from a common claim, but do not refer back to or limit each other. Construing amplification to embrace reverse transcription creates no inconsistency between the two claims. Dependent claim 4 is narrowly drawn to embrace a particular form of amplification (reverse transcription), while dependent claim 7 is broader and embraces all forms of amplification.

In addition to their arguments concerning the disclosures of the asserted patents, Staff and Bio-Rad also cite prior art references discussing reverse-transcription PCR ("RT-PCR"). Of these references, U.S. Patent Application No. 2011/0053798 ("'798 application") is typical.[15] As described in the application, RT-PCR is a two-step process. '798 application, ¶ 0054. The first step is "forming complementary DNA copies of RNA" through reverse transcription. *Id.* The second step is "PCR amplification using the complementary DNA as a template." *Id.* According

[15] The '798 application is attached to Bio-Rad's initial brief as Exhibit RXM-0013.

to Staff and Bio-Rad, because these references describe amplification as occurring in the second step and not the first step, reverse transcription is not amplification. This argument is unpersuasive. The descriptions do not state that "amplification" occurs in the second step, but that "PCR amplification" occurs in the second step. Amplification using polymerase chain reaction ("PCR") techniques is routinely referred to as "PCR amplification." For example, the '530 patent teaches that "[a]mplification may include PCR amplification," as well as "multiple displacement amplification (MDA), rolling circle amplification and other amplification methods." '530 patent, col. 18:40-43; *see also id.*, col 18:29-34 (stating that polynucleotides may be obtained through "polymerase chain reaction (PCR) amplification," as well as "recombinant cloning, polynucleotide amplification (as generally described in PCT/US99/01705) . . . purification methods (such as purification of genomic DNA or RNA), and synthesis reactions"); '024 patent, col. 22:45-47 ("[I]f PCR amplification is desired . . . ."). Thus, the '798 application's reference to "PCR amplification" in describing the second step of the RT-PCR method indicates only that a specific amplification method is performed in the second step. The reverse transcription reaction performed in the first step may not be "PCR amplification," but this does not mean that reverse transcription is not an amplification reaction.

Moreover, in contrast to the descriptions cited by Staff and Bio-Rad, at least one description of RT-PCR expressly acknowledges that amplification occurs in the reverse transcription step of RT-PCR, as well as the PCR step. U.S. Patent Application No. 2015/0315629 ("'629 application") describes RT-PCR as a two-step reaction in which "the first amplification reaction is reverse transcription," and "[t]he single stranded cDNA produced by reverse transcription is then used for subsequent PCR." '629 application, ¶ 0073.[16]

[16] The '629 application is attached to 10X's initial brief as Exhibit 13.

2. Amplification only requires the creation of one or more copies.

Bio-Rad argues that amplification requires the creation of multiple copies and that the creation of a single copy is not amplification. Such a construction is inconsistent with the claims of the '024 patent. Claim 1 of the '024 patent is directed to a droplet with "a target nucleic acid analyte" and a gel bead with "at least 1,000,000 oligonucleotide molecules comprising barcode sequences." '024 patent, col. 33:57-60. After the oligonucleotide molecules are released from the gel bead, "a given oligonucleotide molecule from said oligonucleotide molecules attaches to said target nucleic acid analyte." *Id.*, col. 33:65-col. 34:3. The "said given oligonucleotide molecule attached to said target nucleic acid analyte" is subjected to nucleic acid amplification to yield "a barcoded target nucleic acid analyte." *Id.*, col. 33:4-7. Thus, claim 1 of the '024 patent uses amplification to refer to the creation of a single copy of a single target nucleic acid.

Although Bio-Rad cites a number of statements in the specifications of the asserted patents in support of its position, these statements indicate only that amplification can be used to create multiple copies of a sequence, not that amplification requires the creation of multiple copies. For instance, while the '204 patent states that amplification can be used for various purposes "including but not limited to generating multiple copies of polynucleotide sequences," it specifically notes that amplification can be used to add "adaptor sequences or barcodes to polynucleotides." '204 patent at col. 31:23-25. As shown with respect to claim 1 of the '024 patent, using amplification to add a barcode sequence to a polynucleotide does not require the creation of multiple copies. Bio-Rad also notes that the specification of the '204 patent teaches that "amplification may be used to increase the quantity of a polynucleotide." '204 patent, col. 24:23-25. The creation of a single copy, however, will increase the quantity of the target polynucleotide.

In a similar vein, Bio-Rad points to the '798 application and argues that the application "describes the amplification as a process to 'form multiple copies of a template.'" RIB at 16 (quoting '798 application, ¶ 0052). Bio-Rad's argument is not supported by the full quotation: "Amplification—a process in which a copy number increases. Amplification may be a process in which replication occurs repeatedly over time to form multiple copies of a template." '798 application, ¶ 0052. Thus, according to the '798 application, the creation of multiple copies of the template is an option, not a requirement, of amplification. *Id.*

Bio-Rad further notes that the methods identified in the patents as examples of amplification methods are used to create multiple copies of a target sequence. RIB at 16. The methods identified in the patents, however, are only examples of amplification reactions and the patents explicitly indicate that "amplification" is not limited to such methods. '530 patent, col. 18:40-43 ("Amplification may include PCR amplification, multiple displacement amplification (MDA), rolling circle amplification and other amplification methods."); '024 patent, col. 25:24-28 ("amplification reactions (*e.g.*, PCR, qPCR, reverse-transcriptase PCR, digital PCR, *etc.*)"); '204 patent, col 31:29-40 ("An suitable amplification method may be utilized, including . . . ."). Even if the patents were interpreted as teaching that the identified methods are the preferred amplification methods, the claims would not be limited to such embodiments. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380-82 (Fed. Cir. 2009) ("Although the patent contemplates that certain animals are '[p]referred animals from which to produce a food product,' that statement does not disavow human animals because it relates to preferred embodiments only; it does not state that all animals covered by the claims must produce a food product.").

3. Claim 1 of the '024 patent does not require amplification to be performed in a droplet.

Although it is not explicitly required by its proposed construction, Bio-Rad contends that the amplification step of claim 1 of the '024 patent must be performed in a droplet. Claim 1 of the '024 patent is directed to a three-step method. The first step requires "providing a droplet" with "a target nucleic acid analyte" and a gel bead with "at least 1,000,000 oligonucleotide molecules comprising barcode sequences." '024 patent, col. 33:57-64. The second step requires the "said oligonucleotide molecules" to be released into "said droplet" and "a given oligonucleotide molecule from said oligonucleotide molecules attach[] to said target nucleic acid analyte." *Id.*, col. 33:65-col. 34:3. In the third step, the "said given oligonucleotide molecule attached to said target nucleic acid analyte" is subjected to nucleic acid amplification to yield "a barcoded target nucleic acid analyte." *Id.*, col. 33:4-7. Bio-Rad argues that all three steps must be performed in a droplet. There is no dispute that the first two steps must be performed in a droplet, but 10X and Staff argue that the third step, an amplification step, can be—but does not have to be—performed in a droplet.

The third step, unlike the first and second steps, makes no reference to the droplet. Bio-Rad argues that because "said given oligonucleotide molecule attached to said target nucleic acid analyte" refers to antecedents in the second step, the third step must also occur in the droplet of the second step. Bio-Rad's argument lacks merit. The requirement that the "said given oligonucleotide molecule attached to said target nucleic acid analyte" be created in a droplet in the second step does not mean that it has to remain in the droplet for all subsequent steps. The use of "comprising" in the preamble of claim 1 indicates that there could be additional steps between the second step and the third step. *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000) ("The phrase 'consisting of' is a term of art in patent law

signifying restriction and exclusion, while, in contrast, the term 'comprising' indicates an open-ended construction. . . . A drafter uses the term 'comprising' to mean 'I claim at least what follows and potentially more.'") (internal citation omitted). Thus the claim would cover a four-step method that included a step wherein the droplet was broken after the second step, but before the third step, so long as all three recited steps are performed. *See id.*

E. "providing"/"said at least 1,000 droplets"/"a plurality of cells"

"providing" ('530 patent, claim 1)	
Party	**Construction**
10X	Plain meaning
Bio-Rad	Indefinite; or, in the alternative, "in one experiment"
Staff	"providing as inputs for a droplet generation process"
"said at least 1,000 droplets" ('530 patent, claim 1)	
Party	**Construction**
10X	"1,000 or more droplets"
Bio-Rad	"said at least 1,000 droplets from one experiment"
Staff	Plain and ordinary meaning
"a plurality of cells" ('530 patent, claim 1)	
Party	**Construction**
10X	"two or more cells"
Bio-Rad	Indefinite; or, in the alternative, "a plurality of cell from the same sample"
Staff	"two or more cells from a common sample (which may be a pooled sample)"

Claim 1 of the '530 patent is directed to a three-step method. The first step requires "providing" at least 1,000 gel beads and "a plurality of cells." '530 patent, col. 47:60-67 & col. 48:58-64. Barcode molecules are attached to each of the gel beads and each of the cells contains polynucleotides. *Id.* The second step requires generating "a plurality of droplets, wherein at least 1,000 droplets of said plurality of droplets each" have "a single gel bead from said plurality of cells" and "a single cell from said plurality of cells." *Id.*, col. 48:60-64. The third step requires using the polynucleotide molecules and barcode molecules to form "a plurality of barcoded polynucleotide molecules" "in each of said 1,000 droplets." *Id.*, col. 48:65-col. 49:4.

Bio-Rad asserts that the terms "providing," "plurality of cells," and "at least 1,000 droplets" render the claim indefinite because the claim "calls for the generation of 1,000 droplets containing specific material but does not describe how or under what circumstances those droplets are formed." RRB at 23. In making this argument, Bio-Rad confuses breadth with indefiniteness. Breadth does not render a claim indefinite. *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1367 (Fed. Cir. 2017 ("[B]readth is not indefiniteness.") (quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005)) (internal quotation marks omitted); Manual of Patent Examining Procedure § 2173.02 ("A broad claim is not indefinite merely because it encompasses a wide scope of subject matter provided the scope is clearly defined."). Standing alone and in the context of the claim, the claim terms identified by Bio-Rad are clear and readily understood "even to lay judges." *Phillips*, 415 F.3d at 1314. Based on the foregoing, I find that Bio-Rad has not shown that claim 1 is indefinite.

Through their proposed constructions, both Staff and Bio-Rad seek to narrow the scope of the claims of the '530 patent. As discussed above, a claim term is to be given its plain and ordinary meaning unless the patentee alters the scope of the term through lexicography or disavowal. *Hill-Rom*, 755 F.3d at 1371. Bio-Rad's proposed constructions of the terms "providing" and "said at least 1,000 droplets" require the claimed method to be performed in "one experiment."[17] According to Bio-Rad, this "construction is most consistent with the plain language of the claim," because "a person of ordinary skill would normally think of the steps in a

[17] Staff has proposed that "providing" be construed to mean "providing as inputs for a droplet generation process." While 10X does not dispute the substance of Staff's proposed construction, it argues that the Staff's proposed construction is unnecessary in view of other claim limitations. CIB at 35-36. "Providing" is not a term of art, but rather an ordinary word that is readily understood by a lay judge. *Phillips*, 415 F.3d at 1314. Accordingly, I agree with 10X that Staff's proposed construction is unnecessary.

method" as being performed in a single experiment. RIB at 32. Thus, Bio-Rad's proposed constructions of the terms "providing" and "at least 1,000 drops" attempt to construe "method" as a single "experiment." As used in the claim, the term "method" is not a term of art, but a legal term. *Nassau Precision Casting Co. v. Acushnet Co.*, 566 Fed. Appx. 933 (Fed. Cir. 2014) (non-precedential). A "method" is a "process" and both "'method' and 'process' have a clear and settled meaning: 'a set of actions, necessarily taken over time.'" *Id.*; *see also Bilski v. Kappos*, 561 U.S. 593, 607 (2010) (relying on definition of "method" as "way or manner of doing anything"); *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972) (defining "a process" as "an act, or a series of acts"); *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1316 (Fed. Cir. 2005) (defining "a process" as "a series of acts.") (quoting *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1378 (Fed. Cir. 2003)) (internal quotation marks omitted); *In re Kollar*, 286 F.3d 1326, 1332 (Fed. Cir. 2002) (defining "a process" as "a series of acts or steps"); MPEP § 2106 ("Process—an act, or a series of acts or steps."). In contrast, as 10X and Staff note, the contours of what would constitute a "single experiment" is not well-defined. CIB at 37-38; SRB at 22 n. 12. Thus, defining "method" as a "single experiment" would only create ambiguity by replacing a term that has clear and well-established meaning with one that does not. *See E-Pass Tech., Inc. v. 3Com Corp.*, 473 F.3d 1213, 1220 (Fed. Cir. 2007) ("[T]he terms courts use to enunciate the proper construction of a claim are not themselves limitations that require interpretation").

Bio-Rad's and Staff's proposed constructions also seek to limit the claimed "plurality of cells," by requiring that the cells be obtained from "the same sample" (Bio-Rad) or "a common sample (which may be a pooled sample)" (Staff). Bio-Rad's proposed construction of "plurality of cells" stems from its proposed constructions of "providing" and "at least 1,000 droplets." RIB at 33-34 ("Just as a person of ordinary skill in the art attempting to determine the boundaries of

the claim would focus on the number 1,000 to indicate components of a single experiment, the person of ordinary skill would limit the undefined term 'plurality of cells' to mean cells from one sample used in that single experiment. That is the way a researcher would think about carrying out a single experiment according to the steps identified."). As discussed above, there is no basis for construing "method" to be a "single experiment." Accordingly, Bio-Rad's proposed construction of "plurality of cells" is rejected.

Staff argues that its proposed construction of "plurality of cells" is necessary in order to give life to the claim's numerical limitations requiring at least 1,000 cells, "at least 1,000 gel beads" and "at least 1,000 droplets." CIB at 37-38.[18] According to Staff, absent a requirement that the plurality of cells be drawn from a common sample, the claim's "numerical requirements would not make sense, as the claim could be infringed simply by 5 unrelated repetitions of a droplet generation process using at least 200 gel beads and least 200 cells, or 10 unrelated repetitions of the process using at least 100 gel beads and 100 cells, or 20 unrelated repetitions of the process using at least 50 gel beads and at least 50 cells, *etc.*" *Id.* Staff's concern about preserving the vitality of claim 1's numerical limitations is ungrounded. As drafted, claim 1 is not satisfied by repeating a process that uses less than required number of cells and gel beads or generates less than the required number of droplets.

The second step of claim 1's three-step method requires the generation of "at least 1,000 droplets," while the third step requires generation of barcoded polynucleotide molecules in each

[18] Both 10X and Staff have proposed constructions of "plurality of cells" which would encompass as few as two cells. While such an interpretation is consistent with plain and ordinary meaning of "plurality," it is not consistent with a later claim limitation requiring the generation of at least 1,000 droplets, wherein each droplet has "a single cell from said plurality of cells." '530 patent, col. 48:59-64. Thus, within the context of claim 1, the claimed "plurality of cells" must comprise at least 1,000 cells.

of the "said at least 1,000 droplets." '530 patent, col. 47:60-67 & col. 48:58-64. This language requires that all of the "at least 1,000 droplets" be generated before the third step of claim is performed on any of "said at least 1,000 droplets." If less than 1,000 droplets are generated in the second step, then there is no "said at least 1,000 droplets" for the third step. *E-Pass*, 473 F.3d at 1222 ("[B]ecause the language of most of the steps of its method claim refer to the completed results of the prior step, E-Pass must show that all of those steps were performed in order."). Claim 2, which depends directly from claim 1, supports this interpretation. Claim 2 requires that "prior to (c) [the third step of claim 1], said plurality of polynucleotide molecules are released from said single cell in each of said at least 1,000 droplets." '530 patent, col. 2:5-7. The added step of claim 2 can only be satisfied if all of the "at least 1000 droplets" are generated before any of the droplets are subjected to the third step. *See Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1373 (Fed. Cir. 2005) (relying on dependent claim's use of the term "a span" to construe independent claim as covering razors with more than one span between razor blades). Interpreting claim 1 otherwise would—as Staff correctly notes—negate the claim's numerical limitations. Such a result is strongly disfavored. *Wasica Finance GmbH v. Cont'l Automotive Sys., Inc.*, 853 F.3d 1272, 1288 n. 10 (Fed. Cir. 2017) ("Construing 'bit sequence' to allow for an empty, zero-bit sequence would effectively remove the 'first bit sequence,' 'second, or third bit sequence,' and 'fourth and final bit sequence' limitations from the claim, as it would make them optional or potentially nonexistent. It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous.") (internal citations omitted); *Bicon Inc. v. Straumann, Co.*, 441 F.3d 945, 950-51 (Fed. Cir. 2006) ("[C]laims are interpreted with an eye toward giving effect to all terms in the claim."). Accordingly, a method that generates less than a 1,000 droplets will not infringe claim 1 irrespective of how many times that method is

performed. *See In re Varma*, 816 F.3d 1352, 1362-64 (Fed. Cir. 2016) (finding that the claim requiring "a statistical analysis request corresponding to two or more selected investments" did not encompass two single-investment analyses conducted *seriatim*, but required two investments to be analyzed at the same time).

10X's arguments to the contrary are unpersuasive. While conceding that "unrelated repetitions of non-infringing processes" would not "constitute a single infringing process," 10X contends that the 1,000-droplet threshold can be met though "multiple runs" so long as the runs "are all done as part of the same process." CRB at 21, 40. As discussed above, such an interpretation is contrary to the language of claims 1 and 2. In support of its positon, 10X points to portions of the specification of the '530 patent, which 10X argues teach that the claimed method can be repeated. *See, e.g.*, '530 patent, col. col. 36:49-50 ("With continued reference to FIG. 2, the methods described above are then repeated . . . ."). 10X's reliance on these portions of the specification is misplaced. First, the cited portions of the specification relate to methods for the "[g]eneration of [n]on-[o]verlapping DNA [f]ragments for [s]equencing," not the claimed method, which is a "method for nucleic acid preparation or analysis." *Compare id.*, col. 36:6-7 *with id.*, col. 47:58-59. Second, while the specification states that the "methods" can be repeated, there is no suggestion that the number of partitions (droplets) used in each repetition can be aggregated. Third, even if the specification disclosed aggregating the number of partitions used in multiple runs of the same method, such a disclosure cannot expand the scope of claim 1. *See Scheonhaus v. Genesco, Inc.*, 440 F.3d 1354, 1359 (Fed. Cir. 2006) ("[W]here a patent specification includes a description lacking a feature, but the claim recites that feature, the language of the claim controls."). As discussed above, the claim language of claim 1 requires

that all of the "at least 1,000 droplets" be formed before the third step is performed on any of the droplets.

Based on the foregoing, I find that claim 1 requires that the step of generating "at least 1,000 droplets" be completed before the third step of forming a "plurality of barcoded polynucleotide molecules" is performed in any of the droplets. With that clarification, I find that the terms "providing," "said at least 1,000 droplets," and "a plurality of cells" recited in claim 1 of the '530 patent should be given their plain and ordinary meaning.

VI. CONCLUSION

For the reasons discussed above, I construe the disputed terms from the asserted patents as follows:

The term "1,000,000 oligonucleotides comprising barcode sequences" recited in claim 1 of the '024 patent and claim 1 of the '468 patent means "1,000,000 oligonucleotide molecules that include, but are not necessarily limited to, barcode sequences."

The term "releasably attached" recited in claim 1 of the '024 patent and claim 1 of the '468 patent means "attached in a manner that allows the attached object to be released."

No construction is necessary for the term "reversibly immobilized" recited in claim 15 of the '024 patent.

The term "amplification" recited in claims 1 and 8 of the '024 patent and claims 2 and 21 of the '468 patent; the term "amplifying" recited in claim 11 of the '468 patent and claim 6 of the '530 patent; and the term "amplify" recited in claim 10 of the '024 patent means "increasing the number of copies of the target sequence to be detected." The copies can be exact copies or complementary copies. Reverse transcription is a form of amplification if a cDNA sequence is the target sequence to be detected. Amplification only requires the creation of one or more copies of a template.

The amplification step of claim 1 of the '024 patent can be—but does not have to be—performed in a droplet.

The terms "providing," "said at least 1,000 droplets," and "a plurality of cells" recited in claim 1 of the '530 patent should be given their plain and ordinary meaning. As a point of clarification, the step of generating "at least 1,000 droplets" must be completed before "a plurality of barcoded polynucleotide molecules" is formed in any of the "said at least 1,000 droplets."

Hereafter, discovery and briefing in this Investigation shall be governed by the construction of the claim terms in this Order.

SO ORDERED.

Dee Lord
Administrative Law Judge

CERTAIN MICROFLUIDIC SYSTEMS AND COMPONENTS THEREOF AND PRODUCTS CONTAINING SAME

Inv. No. 337-TA-1100

PUBLIC CERTIFICATE OF SERVICE

I, Lisa R. Barton, hereby certify that the attached **ORDER** has been served by hand upon the Commission Investigative Attorney, **Monica Bhattacharyya, Esq.**, and the following parties as indicated, on **October 31, 2018.**

Lisa R. Barton, Secretary
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- ☐ Other: _____

On Behalf of Respondents Bio-Rad Laboratories, Inc.:

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- ☐ Via Hand Delivery
- ☑ Via Express Delivery
- ☐ Via First Class Mail
- ☐ Other: _____