UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

PACIFIC BIOSCIENCES OF CALIFORNIA, INC., *Plaintiff*, vs. OXFORD NANOPORE TECHNOLOGIES, INC. and OXFORD NANOPORE TECHNOLOGIES, LTD. *Defendant*.	C. A. No. 17-cv-1353-LPS JURY TRIAL DEMANDED

THIRD AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Pacific Biosciences of California, Inc. ("Plaintiff" or "PacBio") for its Third Amended Complaint against Defendants Oxford Nanopore Technologies, Inc. ("ONT, Inc.") and Oxford Nanopore Technologies, Ltd. ("ONT, Ltd.") ("collectively Defendants") alleges and states the following:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the United States Patent Act, 35 U.S.C. §§1, *et seq*., including 35 U.S.C. § 271.

2. PacBio brings this action to halt Defendants' infringement of PacBio's rights under the Patent Laws of the United States 35 U.S.C. § 1, *et seq*., which arise under U.S. Patent Nos. 9,678,056 (the "'056 patent," attached as Exhibit 1), 9,738,929 (the "'929 patent," attached as Exhibit 2), and 9,772,323 (the "'323 patent") (attached as Exhibit 33).

THE PARTIES

3. PacBio is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1305 O'Brien Drive, Menlo Park, California 94025.

4. PacBio was founded in the year 2000 and develops, manufactures, and sells a novel DNA sequencing platform that helps researchers resolve genetically complex problems. PacBio's DNA sequencing technology is based on real-time detection of the incorporation of nucleotides into a single strand of DNA. That technology goes by the name "SMRT®" sequencing, which is short for "Single Molecule, Real-Time" sequencing. PacBio's SMRT® sequencing platform encompasses not just DNA sequencing instruments, but also novel sequencing chips and chemical reagents for use with PacBio's DNA sequencing instrument and sophisticated software for analyzing the data that emerges from PacBio's sequencing instruments.

5. PacBio's SMRT® Sequencing Platform and technology allows researchers to carry out numerous applications, including at least: (1) de novo genome assembly to finish genomes in order to more fully identify, annotate, and decipher genomic structures; (2) targeted sequencing to more comprehensively characterize genetic variations; and (3) identification of DNA base modifications to help characterize epigenetic regulation and DNA damage. PacBio's SMRT® Sequencing Platform and technology provides high-accuracy, ultra-long reads and uniform coverage, and is believed to be the only DNA sequencing technology that provides the ability to simultaneously detect epigenetic changes.

6. In addition to the commercialization of its flagship SMRT® sequencing platform, PacBio has broad expertise in single-molecule sequencing and is engaged in exploratory work

related to single-molecule sequencing, including techniques related to single-molecule sequencing based on detection platforms such as nanopores. Collectively, PacBio's research and development efforts have resulted in a patent portfolio that includes over 330 issued U.S. patents and pending applications related to single-molecule sequencing techniques.

7. Defendant ONT, Inc. is a corporation organized under the laws of Delaware with its principal place of business at 1 Kendall Square, Bldg. 200, Cambridge, Massachusetts 02139. On information and belief, ONT, Inc. is engaged in the commercialization throughout the United States of nanopore-based single-molecule sequencing products, including at least the MinION, GridION X5, PromethION, SmidgION, and Flongle sequencing instruments, reagents and kits for use with these instruments, and the 2D and 1D Squared products.

8. Defendant ONT, Ltd. is the corporate parent of ONT, Inc. and is a corporation organized under the laws of England and Wales with its principal place of business at Edmund Cartwright House, 4 Robert Robinson Avenue, Oxford Science Park, Oxford, OX4 4GA, UK. On information and belief, ONT, Ltd. is engaged in the design, manufacture, importation into the United States, sale for importation, and commercialization throughout the United States of nanopore-based single-molecule sequencing products, including at least the MinION, GridION X5, PromethION, SmidgION, and Flongle sequencing instruments, reagents and kits for use with these instruments, and the 2D and 1D Squared products.

JURISDICTION AND VENUE

9. This action arises under the Patent Laws of the United States, Title 35, United States Code, §§ 1 *et seq*., including 35 U.S.C. §§ 271 and 281.

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over defendant ONT, Inc. ONT, Inc. has substantial contacts with the forum as a consequence of conducting business in Delaware, and has purposefully availed itself of the benefits and protections of Delaware state law by incorporating under Delaware law.

12. This Court also has personal jurisdiction over ONT, Ltd. ONT, Ltd. has purposefully availed itself of the benefits of Delaware's laws and of the privilege of conducting business in Delaware by directing into Delaware products that embody the patents-in-suit. ONT, Ltd. for instance has broadly targeted the United States as a market for its products and, as part of these efforts, has specifically targeted the Delaware market, including Delaware organizations and companies such as the University of Delaware, DuPont, and AstraZeneca. Upon information and belief, in addition to making its products available for purchase in Delaware through its website, ONT, Ltd. and its staff have specifically identified Delaware organizations as potential customers for its products and have successfully reached out to these customers and placed their products with these customers and subsequently provided particularized support services and received feedback.

13. For instance, upon information and belief, ONT, Ltd. has provided genetics laboratories at the University of Delaware with its sequencing products. One laboratory at the University of Delaware claims to have as a member a "resident expert" on Defendants' MinION sequencing platform. *See* Exhibit 39. Upon information and belief, in connection with the provision of its sequencing products to the University of Delaware, ONT, Ltd. has contracted with the University of Delaware and/or Delaware residents affiliated with the University of Delaware to impose terms and conditions upon their receipt and use of Defendants' sequencing equipment. Attached hereto as Exhibits 40 and 41 are exemplary agreements governing the

relationship between ONT, Ltd. and its Delaware customers. Among other things, these agreements impose restrictions on how Defendants' equipment may be used, grants license rights, imposes confidentiality duties, grants audit rights, provides for supports services, and limits publication rights. These agreements are expressly between Defendants' customers and ONT, Ltd. and thus show that ONT, Ltd. has actively engaged in business in this district and taken an active role in governing its relationship with its Delaware customers.

14. Additionally, upon information and belief, ONT, Ltd.'s highest-ranking business development corporate officers have specifically contacted individuals at Delaware organizations and entities (such as the University of Delaware and DuPont) to inter alia enter into research collaborations, provide product status updates, receive product feedback, provide technical support, share research results, and arrange for in-person meetings. On the foregoing bases, ONT, Ltd. has had substantial contacts with this jurisdiction sufficient to subject it to jurisdiction in this district.

15. At a minimum, this Court has jurisdiction over ONT, Ltd. because ONT, Inc. and ONT, Ltd. are alter egos and/or agents of each other in connection with performance of the infringing acts below. Upon information and belief, the following facts, in addition to those contained in the rest of this complaint, demonstrate that ONT, Inc. and ONT, Ltd. share a unified governance, interest, and ownership in connection with the infringing acts identified below such that to the extent the Court exercises jurisdiction over ONT, Inc., it may also exercise jurisdiction over ONT, Ltd.

16. Upon information and belief, ONT, Ltd. and ONT, Inc. share overlapping officers and there is no meaningful distinction in the governance of the two entities. For instance, in addition to acting as both the President and a Director of ONT, Inc., Spike Willcocks serves as

the Chief Business Development Office of ONT, Ltd. Likewise, in addition to acting as Treasurer, Secretary, and Director of ONT, Inc., James McDonald acts the Vice President of Finance for ONT, Ltd. Upon information and belief, the day-to-day activities of ONT, Inc. are effectively governed by ONT, Ltd. such that there is effectively no distinction between the two corporate entities.

17. Consistent with the foregoing, upon information and belief, the highest-ranking officers of ONT, Inc. either self-identify on social media as officers of ONT, Ltd. or make no distinction between the two different ONT companies, confirming that ONT, Inc. and ONT, Ltd. are effectively alter egos. Attached as Exhibits 42, 43, and 44 are the LinkedIn profiles of the official officers of ONT, Inc. (Sissel Juul, Spike Willcocks, and James Brayer) showing that none identify themselves as employees of ONT, Inc.

18. As yet further confirmation that there is effectively no distinction between ONT, Inc. and ONT, Ltd., there is no distinct website for ONT, Inc. All of Defendants' United States locations—including any locations ostensibly affiliated with ONT, Inc.—are portrayed on Defendants' website as being part of a single unified entity under the umbrella of the primary ONT, Ltd. location in England. Consistent with this, Defendants' website offers a single unified contact point for inter alia purchase inquiries, support inquiries, employment inquiries, product information, and company news updates. Attached as Exhibit 45 is an excerpt from Defendants' website showing how their different locations are portrayed in a unified manner.

19. As yet another example, upon information and belief, ONT, Inc. and ONT, Ltd. share the same internal and external legal counsel. In connection with both this litigation and ongoing ITC litigation involving ONT, Ltd., Defendants' are represented by outside counsel at Baker Botts LLP. Likewise, upon information and belief, this litigation has been managed not

by a dedicated ONT, Inc. employee, but by James McDonald, ONT, Ltd.'s Vice President of Finance.

20. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c), and 1400(b) because (1) ONT, Inc. is a Delaware corporation, (2) ONT, Ltd. is an alien corporation subject to venue in any district and (3) Delaware is a convenient forum for resolution of the parties' disputes set forth herein.

BACKGROUND

21. On information and belief, in the 2015 timeframe, Defendants began commercializing single-molecule sequencing products based on the use of protein nanopores. Defendants purport to offer a single-molecule sequencing product that, like PacBio's products, is capable of determining the sequence of long stretches of DNA in a single pass. The ability to generate such "long reads" is an area where PacBio has and continues to be widely recognized as the technical and commercial leader. PacBio and Defendants compete in the single-molecule sequencing market.

22. Defendants' single-molecule sequencing products include at least the MinION, GridION X5, PromethION, SmidgION, and Flongle sequencing systems and reagents, consumables, and software for use with same, including without limitation reagents and kits used to generate "2D reads" and "1D squared reads" using Defendants' sequencing instruments (collectively, the "Accused Products"). For example, two views of a representative MinION device are shown below:

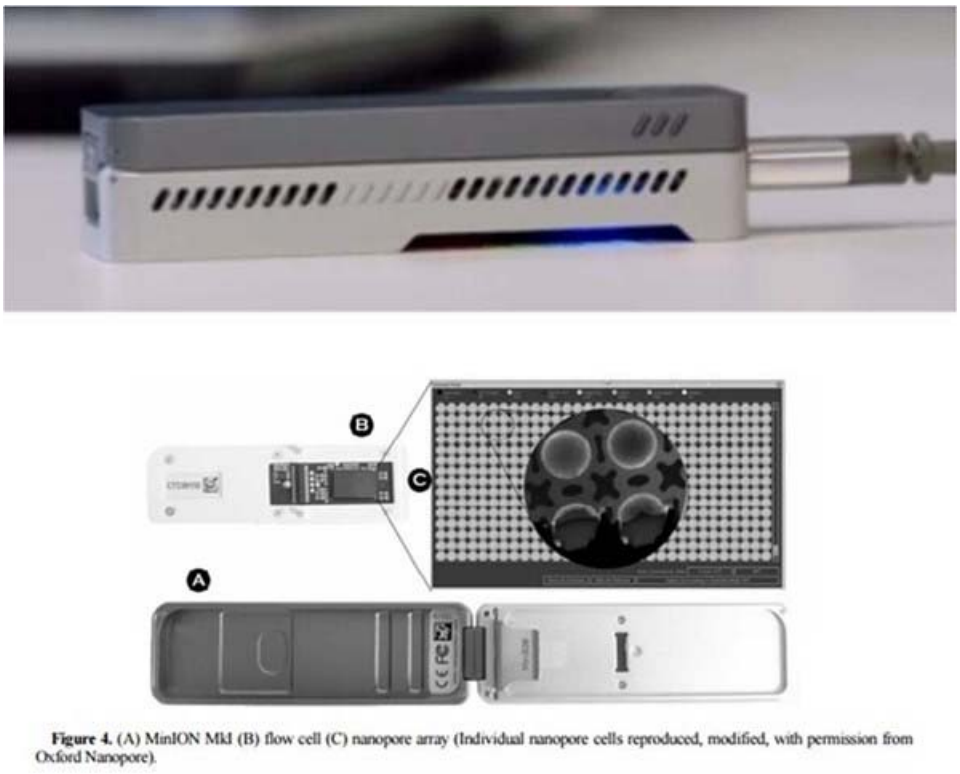

Figure 4. (A) MinION Mk1 (B) flow cell (C) nanopore array (Individual nanopore cells reproduced, modified, with permission from Oxford Nanopore).

Exhibit 5; Exhibit 6 at 292. The top image shows a working MinION device, and the bottom view shows the interior of the device. The portion labeled "C" in the above photograph depicts a flow cell with an array of individual nanopores. Nanopores are tiny holes embedded into a membrane and are formed by inserting proteins that have a hollow tube through their center into a polymer membrane, as shown in the image below:

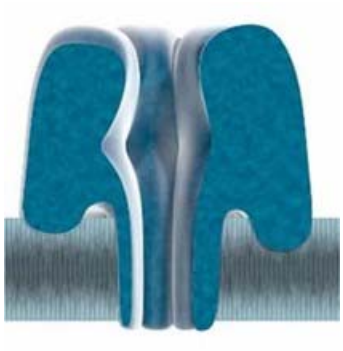

Exhibit 7. The Accused Products each include one or more flow cells that include a "nanopore array."

23. While the MinION instrument includes a single flow cell, the PromethION instrument includes 48 flow cells and has been described as a "whole box of MinION sequencers." Exhibit 8. A representative PromethION instrument with its 48 flow cells is shown below:

Id.

24. Similarly, the GridION X5 is an instrument that is described by Oxford as containing "up to five MinION Flow Cells." Exhibit 15. A representative GridION X5 instrument with its 5 flow cells is shown below:

Id.

25. The SmidgION is an instrument that contains a single flow cell. Defendants' describe the SmidgION as "us[ing] the same core nanopore sensing technology as MinION" in a "smaller device" "for use with smartphones or other mobile, low power devices." Exhibit 14. A representative image of the SmidgION instrument is shown below:

Id.

26. The Flongle is an adapter intended to be used with MinION and GridION devices. Defendants describe the Flongle as "an adapter (flow cell dongle) for MinION or GridION that

enables direct, real-time DNA or RNA sequencing on smaller, single-use flow cells." "Flongle uses the same core nanopore technology as MinION, GridION and PromethION, offering direct DNA or RNA analysis, simple preparation, real-time data and long reads." Exhibit 35. A representative image of the Flonge is shown below:

Id.

27. To sequence DNA using any one of the Accused Products, one first applies a voltage across the membrane such that an electrical current flows through the hole. A strand of DNA is then drawn through the hole:

Exhibit 9. As the DNA passes through the hole, it disrupts the electrical current that is passing through the hole, thus producing a signal. To evaluate the sequence, one can attempt to correlate this signal with the DNA bases that are passing through the hole.

28. Defendants, however, have asserted in parallel litigation proceedings that nanopore sequencing was not known in the 2008-2009 timeframe and/or that nanopore sequencing was not enabled to the skilled artisan. For instance, Defendants have asserted in the International Trade Commission that "nanopore sequencing was not known in 2008 and is a later developed technology." Ex. 29 [Mtn. for Leave] at 9 n. 11. Likewise, Defendants have asserted that in the 2008 - 2009 timeframe "nanopore sequencing was not considered a viable single molecule sequencing approach." Ex. 30 [Petition Response] at 34.

29. Defendants' products therefore have incorporated a number of inventive concepts developed by researchers at PacBio that have helped make nanopore sequencing a viable approach.

30. For instance, in nanopore-based DNA sequencing systems, such as the Accused Products sold by Defendants, the signal that results from passage of the DNA through the nanopore arises not just from a single DNA base, but from a contiguous group of DNA bases that interacts with the nanopore at a given time. Therefore, to determine the DNA sequence, the software made available by Defendants for use with the Accused Products uses calibration information produced by measuring the signals from the different combinations of bases that may interact with the nanopore at a given time. This innovation was conceived of by researchers at PacBio and is described in the '323 patent and its parent U.S. Patent No. 9,546,400.

31. As another example, to increase accuracy, Defendants' products utilize at least two motor proteins consisting of modified enzyme that modulates the rate of translocation,

allowing one to better capture the signals that arise from the nanopore. This innovation was conceived of by researchers at PacBio and is described in the '056 patent.

32. As yet another example, Defendants use techniques based on redundant sequencing in which one sequences complementary strands of DNA in a nanopore to generate a consensus sequence. Inventive techniques for using this approach with nanopores were conceived of by researchers at PacBio and are described in the '929 patent. Defendants have characterized this technique in particular as offering "major advantages." For instance, in one of their patent filings, Defendants stated "linking the two strands of the target polynucleotide by a bridging moiety allows both strands of the target polynucleotide to be sequenced by the transmembrane pore. This method is advantageous because it doubles the amount of information obtained from a single double stranded target polynucleotide construct. Moreover, because the sequence in the complementary 'anti-sense' strand is necessarily orthogonal to the sequence of the 'sense' strand, the information from the two strands can be combined informatically. Thus, this mechanism provides an orthogonal proof-reading capability that provides higher confidence observations." Ex. 28 [2016/0281159] ¶ 71. Defendants' patent application goes on to describe yet additional advantages of this approach. *Id*. ¶¶ 72-74.

COUNT I

(Infringement of U.S. Patent No. 9,678,056)

33. Plaintiff repeats and re-alleges each and every allegation contained in the preceding paragraphs of this Complaint as if stated in their entirety herein, and incorporates them herein by reference.

34. The '056 patent, entitled "Control of Enzyme Translocation in Nanopore Sequencing," was issued on June 13, 2017, to inventors Steven Turner and Benjamin Flusberg.

The ’056 patent is assigned on its face to Plaintiff PacBio. PacBio is the owner of all rights, title to and interest in the ’056 patent.

35. Defendants infringe, literally or under the doctrine of equivalents, both directly and indirectly (by inducement and by contribution), PacBio’s ’056 patent through their activities connected to at least the Accused Products.

36. On information and belief, Oxford Defendants have directly infringed and continue to directly infringe at least claim 1 of the ’056 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by using within the United States without authority the Accused Products. As an example, attached as Exhibit 3 is a preliminary and exemplary claim chart detailing Defendants’ infringement of this claim of the ’056 patent. This chart is not intended to limit PacBio’s right to modify the chart or allege that other products and/or activities of Oxford infringe the identified claim or any other claims of the ’056 patent or any other patents. Exhibit 3 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 3 that is mapped to Defendants’ Accused Products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

37. For instance, claim 1 of the ’056 patent is listed below:

> A method for sequencing a nucleic acid template comprising:
>
> [a] providing a substrate having an upper solution above the substrate, a lower solution below the substrate, the substrate comprising a nanopore connecting the upper solution and lower solution, the nanopore sized to pass a single strand of nucleic acid;
>
> [b] providing a voltage across the nanopore to produce a measurable current flow through the nanopore;
>
> [c] controlling the rate of translocation of a single stranded portion of the nucleic acid template through the nanopore with a translocating enzyme that is associated with the nucleic acid template under reaction

> conditions whereby the translocating enzyme and the reaction conditions are selected such that the translocating enzyme exhibits two kinetic steps wherein each of the kinetic steps has a rate constant, and the ratio of the rate constants of the kinetic steps is from 10:1 to 1:10;
>
> [d] measuring the current through the nanopore over time as the nucleic acid template is translated through the nanopore; and
>
> [e] determining the sequence of a portion of the nucleic acid template as it translates through the nanopore using the measured current over time.

38. Use of Defendants' products leads to direct infringement of this claim in at least the following way: Defendants' products include a nucleic acid sequencing instrument having a substrate, which is a nanopore in a membrane, and an upper solution above the membrane and a lower solution below the membrane (step a). Nucleic acid molecules are sequenced by passing a nucleic acid molecule strand through the nanopore, which connects the upper and lower solutions and is sized to pass a single strand of nucleic acid through. A voltage is then applied across the membrane to drive a current across the membrane (step b). The rate of translocation of a single stranded portion of the nucleic acid template through the nanopore is controlled via a translocating enzyme that is associated with the nucleic acid template under reaction conditions. The translocating enzyme exhibits two steps where the rate constant for portions of the template molecule translocation would fall within the claimed range of 10:1 to 1:10 (step c). The current through the nanopore is measured over time as the nucleic acid template is translated through the nanopore (step d). As a nucleic acid molecule to be sequenced is drawn through the nanopore, the current is disrupted and measured using an ASIC chip which is part of the sequencing instrument. The sequence of the nucleic acid template is then determined using Defendants' basecalling software, based on the current measurements as the nucleic acid template is translated through the nanopore (step d).

39. On information and belief, Defendants have monitored PacBio's patent filings and has been aware of the '056 patent since its issuance on June 13, 2017. At a minimum, Defendants have had knowledge of and notice of the '056 patent and its infringement since at least, and through, the filing and service of PacBio's complaint in this action and despite this knowledge continues to commit the aforementioned infringing acts.

40. Defendants actively, knowingly, and intentionally have induced, or have threatened to induce, infringement of at least claim 1 of the '056 patent through a range of activities. First, on information and belief, Defendants have induced infringement by controlling the design and manufacture of, offering for sale, and selling the Accused Products with the knowledge and specific intent that their customers will use the Accused Products to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants have admitted in an ongoing International Trade Commission investigation that it imports, sold for importation, and or/sells their MinION product and PromethION product within the United States. *See* Exhibit 10 ¶ 53.

41. Second, on information and belief, Defendants have induced infringement by their customers through the dissemination of promotional and marketing materials relating to the Accused Products with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants promote the Accused Products on their website, stating that their products offer numerous benefits such as real-time DNA/RNA sequencing, no capital cost, long reads, scalability, high-fidelity, and rapid library preparation time. *See* Exhibit 11.

42. Third, on information and belief, Defendants have induced infringement by their customers through the creation of distribution channels for the MinION and/or GridION instruments in the United States with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants' website allows customers in the United States to purchase starter packs of Defendants' MinION and GridION X5 instruments that, when used, will lead to infringement of the '056 patent. As Defendants' website states, "[b]uy a Starter Pack to join the growing numbers in the Nanopore Community." *See* Exhibit 12. As another example, Defendants have created an early access program for their PromethION instrument that provides access to a PromethION device, site installation support, flow cells and reagents, and further information and support. *See* Exhibit 13. As another example, Defendants' website allows potential customers in the United States to register their interest in Defendants' SmidgION instrument, so that they can "be one of the first to start using SmidgION." Exhibit 14. Most recently, Defendants have announced that it "plan[s] to release Flongle into early access followed by release to general users within 2018." Exhibit 35.

43. Fourth, on information and belief, Defendants have induced infringement through the distribution of other instructional materials, product manuals, and technical materials with the knowledge and the specific intent to encourage and facilitate their customer's infringing (either literally or under the doctrine of equivalents) use of the Accused Products. Defendants are liable for their induced infringement of the '056 patent pursuant to 35 U.S.C. § 271 (b).

44. Defendants have contributed to, or have threatened to contribute to, the infringement by their customers of the '056 patent by, without authority, selling and offering to

sell within the United States materials and apparatuses for practicing the claimed invention of the '056 patent, including, at least, the Accused Products. When, for example, any of the Accused Products is used by Defendants' customers for nucleic acid sequencing, the claimed method of the '056 patent for sequencing a nucleic acid template is performed, thereby infringing, literally or under the doctrine of equivalents, at least claim 1 of the '056 patent.

45. On information and belief, Defendants know that the Accused Products each constitute a material part of the inventions of the '056 patent and that they are not a staple article or commodity of commerce suitable for substantial noninfringing use. As documented above, the Accused Products consist of specialized substrates containing protein nanopores that are used in conjunction with specialized reagents for the purpose of sequencing nucleic acid templates. *See supra* ¶¶ 21-37. As such, none of the Accused Products nor any of the reagent kits for use with the Accused Products is a staple article of commerce suitable for substantial non-infringing use. Defendants know that the Accused Products are not staple articles or commodities of commerce suitable for substantial non-infringing use because the Accused Products have no use apart from infringing the '056 patent. Defendants are liable for their contributory infringement of the '056 patent pursuant to 35 U.S.C. § 271(c).

46. Defendants' infringement of the '056 patent has injured PacBio in its business and property rights. PacBio is entitled to recover monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial. Defendants' infringement of the '056 patent has caused irreparable harm to PacBio and will continue to cause such harm unless and until Defendants' infringing activities are enjoined by this Court.

COUNT II

(Infringement of U.S. Patent No. 9,738,929)

47. Plaintiff repeats and re-alleges each and every allegation contained in the preceding paragraphs of this Complaint as if stated in their entirety herein, and incorporates them herein by reference.

48. The ’929 patent, entitled “Nucleic Acid Sequence Analysis,” was issued on August 22, 2017, to inventors Stephen Turner, Jon Sorenson, Kenneth Mark Maxham, John Eid, Cheryl Heiner, and Kevin Travers. The ’929 patent is assigned on its face to Plaintiff PacBio. PacBio is the owner of all rights, title to and interest in the ’929 patent.

49. Defendants infringe, literally or under the doctrine of equivalents, both directly and indirectly (by inducement and by contribution), PacBio’s ’929 patent through their activities connected to at least the Accused Products when used with at least Defendants’ kits and reagents for generating “2D reads” and “1D squared reads.”

50. On information and belief, Defendants have directly infringed and continue to directly infringe at least claims 1, 2, 6-7, 8, and 10-11 of the ’929 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by using within the United States without authority the Accused Products when used with at least Defendants’ kits and reagents for generating “2D reads” and “1D squared reads.” As an example, attached as Exhibit 4 is a preliminary and exemplary claim chart detailing Defendants’ infringement of these claims of the ’929 patent. This chart is not intended to limit PacBio’s right to modify the chart or allege that other products and/or activities of Defendants infringe the identified claim or any other claims of the ’929 patent or any other patents. Exhibit 4 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 4 that is mapped to Defendants’ Accused Products shall be

considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

51. For instance, claim 1 of the ’929 patent is listed below:

> A method of determining a nucleotide sequence of a region of interest in a polynucleotide, the method comprising:
>
> [a] introducing a polynucleotide comprising a region of interest to a sequence analysis system comprising a nanopore in a membrane, wherein the polynucleotide comprises a double-stranded portion comprising complementary strands of the region of interest;
>
> [b] applying a voltage across the membrane;
>
> [c] monitoring variations in ionic current through the nanopore of the sequence analysis system during enzyme chaperone-regulated passage of the polynucleotide through the nanopore;
>
> [d] analyzing the monitored variations in ionic current to obtain nucleotide sequence information for the polynucleotide, wherein the nucleotide sequence information comprises redundant sequence information for the region of interest, wherein the redundant sequence information comprises the nucleotide sequence of the complementary strands; and
>
> [e] determining a consensus sequence for the region of interest based on the redundant sequence information.

52. The claims of the ’929 patent are not directed to the patent-ineligible abstract idea of medical screening by comparing wild-type genetic sequences with a subject’s genetic sequence to see if there is a difference. Nor are the claims of the ’929 patent directed to the law of nature that there is a relationship between the sequences of two strands of double-stranded DNA.

53. Rather, the claims of the ’929 patent are directed to the patent-eligible subject of an improved nanopore DNA sequencing process that helps determine an unknown DNA sequence for a region of interest. It employs a nanopore-based DNA sequencing technique in which a consensus sequence is determined by analyzing dual signals that arise from both strands

of a double-stranded DNA template. This process, and the double-stranded DNA structures used within this process, use the relationship between the sequences of two strands of doublestranded DNA to compensate for inaccuracies inherent in nanopore-based DNA sequencing and represented major improvements to such techniques, which were emerging in the 2008-2009 time-frame.

54. Use of Defendants' products leads to direct infringement of the '929 patent in at least the following way: Defendants' products include a sequence analysis system having a nanopore in a membrane (step a). A double-stranded polynucleotide is sequenced by unzipping the double strand to form a long single strand which is fed through the nanopore. A voltage is then applied across the membrane to drive a current across the membrane (step b). An enzyme regulates the passage of the polynucleotide through the nanopore, and variations in the ionic current through the nanopore of the sequence analysis system is measured and monitored (step c). The sequence of the polynucleotide is then determined using Defendants' basecalling software, based on the variations in the monitored ionic current as the polynucleotide is passed through the nanopore. As set forth above in paragraph 18, Defendants have asserted in parallel litigation that nanopore sequencing was not known in the 2008-2009 time frame, when the applications to which the '929 claim priority were filed. Accepting Defendants' assertions as true, nanopore DNA sequencing technology as recited in steps a-c of claim 1 of the '929 patent cannot be regarded as generic, well-understood, well-known, conventional, or a "well-known technological environment" in the 2008-2009 time frame.

55. When Defendants' sequencing instruments are used with Defendants' kits and reagents for generating either "2D reads" or "1D squared reads," redundant sequence information is generated and the analysis uses redundant sequence information including the

sequence information from the sense and antisense strands of DNA (step d). Based on the analysis of redundant sequence information, a consensus sequence is determined (step e).

56. The double-stranded polynucleotide structures used in the claims of the '929 patent (including without limitation in claims 1, 6-8 and 10-11) and the use of such structures to generate redundant sequence information and consensus sequence information represent inventive concepts that improved upon nanopore-based DNA sequencing techniques by dramatically increasing the accuracy of such techniques and change the way the actual sequencing process is performed. Defendants have already acknowledged this in its own patent filings, such as U.S. Patent Application Publication 2016/0281159, entitled *Hairpin Loop Method for Double Strand Polynucleotide Sequencing Using Trasmembrane Pores*. As explained above in paragraph 22, Defendants explain in this patent filing the major improvements such techniques offer.

57. As another example, during the prosecution of another patent application entitled *Adaptors for Nucleic Acid Constructs in Transmembrane Sequencing*, Defendants have stated as follows:

> **Linking the two strands of a double stranded nucleic acid template with a hairpin-containing adaptor prior to sequencing provides a number of surprising and unexpected advantages that are neither taught nor disclosed by the cited references**. Interrogating each position in the original template nucleic twice (once on the sense strand and once on the antisense strand) gives greater certainty that each position in the nucleic acid has been observed. Combining the current data for each position in the sense and anti-sense strands generates an aggregate call of a greater quality score than would be possible with a single observation. This ensures that the quality of the sequence data generated is much higher, with a reduced potential for misidentified base calls or completely missed bases. **As discussed at the bottom of page 10 of the specification as filed, being able to interrogate each base twice is particularly important for sequencing using nanopore sensing**:

> The ability to interrogate each position twice also provides other advantages, such as differentiation between methylcytosine and thymine. These two bases result in similar current traces when they pass through a transmembrane pore and so it can be difficult to differentiate between them. However, interrogation of each position in a nucleic acid twice allows such differentiation because the complementary base for methylcytosine is guanine, whereas the complementary base for thymine is adenine.

Ex. 31 at 11-12; Ex. 32 ¶ 74. By these statements, Defendants have acknowledged that the double-stranded polynucleotide structures used in claims 1, 6-8 and 10-11 and the use of such structures to generate redundant sequence information and consensus sequences represent inventive concepts that improved upon nanopore-based DNA sequencing techniques. Indeed, Defendants attempted to patent this inventive concept for themselves to use as an improvement in nanopore sequencing. *See* Ex. 31 at 2 ("combining the current data from the sense and antisense strands obtained in step (d) to generate a higher quality aggregate call for both bases at each position as compared with a single observation").

58. As yet another example, Defendants' patent application documents a "dumbbell structure" that has complementary regions of DNA that can be used to generate consensus sequence information:

> FIG. 6 shows the treatment of the captured dumbbell structure (FIG. 1, A) with the enzyme encoded in the hybridised region of the Type II adaptor releases a covalently closed structure as depicted here (left). Treatment of this structure with a denaturant yields a single stranded structure (right) susceptible to exonuclease I digestion, which if processive, will liberate nucleotides from the DNA to be interrogated, the linking artificial sequence nucleotides and then the reverse complement nucleotides, which can be compared with the base calls already made. Combination of the calls generates a consensus call of greater quality.

Ex. 32 ¶ 49. By these statements, Defendants again acknowledge that the double-stranded polynucleotide structures used in claims 1, 6-8 and 10-11 and the use of such structures to generate redundant sequence information and consensus sequence information represent inventive concepts that improved upon nanopore-based DNA sequencing techniques.

59. Claims 6 and 7 are directed to the use of double-stranded polynucleotide sequences that have greater than 75% and greater than 90% complementary, respectively. The use of polynucleotides with such physical structures represents an inventive concept that improved upon nanopore-based DNA sequencing techniques because it allows one to generate consensus sequence over at least 75% of the DNA that is being analyzed, which improves the accuracy of nanopore-based DNA sequencing techniques.

60. Claims 8, 10, and 11 are directed to the use of double-stranded polynucleotide sequences where the strands are linked (claim 8), where the linker comprises a "nucleotide" (claim 10) and where the linker comprises an "oligonucleotide" (claim 11). Such linked double-stranded structures are not naturally occurring. The use of such linking structures with double-stranded DNA represents yet another inventive concept that improved upon nanoporebased DNA sequencing techniques. Such linking structures ensure that after one strand of the double-stranded DNA is passed through the nanopore, the complementary strand is passed through the next. By ensuring this, the process of generating consensus sequence information in nanopore sequencing is improved because one can confidently link the ionic current signal associated with the forward strand of DNA to the ionic current signal associated with the reverse strand of DNA. Moreover, the use of such linking structures ensures that the signal information from the forward and reverse strands of DNA is derived from the same nanopore. In this regard, the linking structures of the claimed invention offer an improvement specific to nanopore sequencing

because it ensures that the data from the forward and reverse strands of DNA emerges from the same physical and chemical environment, thus allowing for an apples-to-apples comparison. As noted above in paragraphs 47-48, Defendants have acknowledged in its patent filings that such techniques represent inventive concepts that improved nanopore-based DNA sequencing.

61. The claims of the ’929 patent are limited to the context of nanopore-based DNA sequencing and offer improvements specific to this technique, at least by virtue of the fact that they recite a “sequence analysis system comprising a nanopore in a membrane.” As such, the claims of the ’929 patent do not preempt a law of nature.

62. On information and belief, Defendants have monitored PacBio’s patent filings and has been aware of the ’929 patent since its issuance on August 22, 2017. At a minimum, Defendants have had knowledge of and notice of the ’929 patent and its infringement since at least, and through, the filing and service of PacBio’s complaint in this action and despite this knowledge continues to commit the aforementioned infringing acts.

63. Defendants actively, knowingly, and intentionally have induced, or have threatened to induce, infringement of at least claim 1 of the ’929 patent through a range of activities. First, on information and belief, Defendants have induced infringement by controlling the design and manufacture of, offering for sale, and selling the Accused Products with the knowledge and specific intent that their customers will use the Accused Products to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants have admitted in an ongoing International Trade Commission investigation that it imports, sold for importation, and or/sells their MinION product and PromethION product within the United States. *See* Exhibit 10 ¶ 53.

64. Second, on information and belief, Defendants have induced infringement by their customers through the dissemination of promotional and marketing materials relating to the Accused Products with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants promote the Accused Products on their website, stating that their products offer numerous benefits such as real-time DNA/RNA sequencing, no capital cost, long reads, scalability, high-fidelity, and rapid library preparation time. *See* Exhibit 11.

65. Third, on information and belief, Defendants have induced infringement by their customers through the creation of distribution channels for the MinION and/or GirdION instruments in the United States with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for determining a nucleotide sequence of a region of interest in a polynucleotide. For instance, Defendants' website allows customers in the United States to purchase starter packs of Defendants' MinION and GridION X5 instruments that, when used, will lead to infringement of the '929 patent. As Defendants' website states, "[b]uy a Starter Pack to join the growing numbers in the Nanopore Community." *See* Exhibit 12. As another example, Defendants have created an early access program for their PromethION instrument that provides access to a PromethION device, site installation support, flow cells and reagents, and further information and support. *See* Exhibit 13. As another example, Defendants' website allows potential customers in the United States to register their interest in Defendants' SmidgION instrument, so that they can "be one of the first to start using SmidgION." Exhibit 14. Most recently,

Defendants have announced that it "plan[s] to release Flongle into early access followed by release to general users within 2018." Exhibit 36.

66. Fourth, on information and belief, Defendants have induced infringement through the distribution of other instructional materials, product manuals, and technical materials with the knowledge and the specific intent to encourage and facilitate their customer's infringing (either literally or under the doctrine of equivalents) use of the Accused Products. Defendants are liable for their induced infringement of the '929 patent pursuant to 35 U.S.C. § 271 (b).

67. Defendants have contributed to, or have threatened to contribute to, the infringement by their customers of the '929 patent by, without authority, selling and offering to sell within the United States materials and apparatuses for practicing the claimed invention of the '929 patent, including at least the Accused Products. When, for example, any of the Accused Products is used by Defendants' customers for sequencing a polynucleotide, the claimed method of the '929 patent for determining a nucleotide sequence of a region of interest in a polynucleotide is performed, thereby infringing, literally or under the doctrine of equivalents, at least claim 1 of the '929 patent.

68. On information and belief, Defendants know that the Accused Products each constitute a material part of the inventions of the '929 patent and that they are not a staple article or commodity of commerce suitable for substantial noninfringing use. As documented above, the Accused Products consist of specialized substrates containing protein nanopores that are used in conjunction with specialized reagents for the purpose of determining a nucleotide sequence of a region of interest in a polynucleotide. *See supra* ¶¶ 21-28, 46-54. As such, none of the Accused Products nor any of the reagent kits for use with the Accused Products is a staple article of commerce suitable for substantial non-infringing use. Defendants know that the Accused

Products are not staple articles or commodities of commerce suitable for substantial non-infringing use because the Accused Products have no use apart from infringing the '929 patent. Defendants are liable for their contributory infringement of the '929 patent pursuant to 35 U.S.C. § 271(c).

69. Defendants' infringement of the '929 patent has injured PacBio in its business and property rights. PacBio is entitled to recover monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial. Defendants' infringement of the '929 patent has caused irreparable harm to PacBio and will continue to cause such harm unless and until Defendants' infringing activities are enjoined by this Court.

COUNT III

(Infringement of U.S. Patent No. 9,772,323)

70. Plaintiff repeats and re-alleges each and every allegation contained in the preceding paragraphs of this Complaint as if stated in their entirety herein, and incorporates them herein by reference.

71. The '323 patent, entitled "Nanopore Sequencing Using N-mers," was issued on September 26, 2017, to inventors Steven Turner and Benjamin Flusberg. The '323 patent is assigned on its face to Plaintiff PacBio. PacBio is the owner of all rights, title to and interest in the '323 patent.

72. Defendants infringe, literally or under the doctrine of equivalents, both directly and indirectly (by inducement and by contribution), PacBio's '323 patent through their activities connected to at least the Accused Products.

73. On information and belief, Defendants have directly infringed and continue to directly infringe at least claim 1 of the '323 patent pursuant to 35 U.S.C. § 271(a), literally or

under the doctrine of equivalents, by using within the United States without authority the Accused Products. As an example, attached as Exhibit 34 is a preliminary and exemplary claim chart detailing Defendants' infringement of this claim of the '323 patent. This chart is not intended to limit PacBio's right to modify the chart or allege that other products and/or activities of Defendants infringe the identified claim or any other claims of the '323 patent or any other patents. Exhibit 34 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 34 that is mapped to Defendants' Accused Products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

74. For instance, claim 1 of the '323 patent is listed below:

> A method for sequencing template nucleic acids comprising:
>
> [a] providing a device comprising an array of nanopores a in contact with a solution, the solution comprising a plurality of template nucleic acids above the nanopore;
>
> [b] providing a voltage across the nanopores, whereby, for one or more nanopore in the array, a template nucleic acid is translocated through the nanopore, wherein the translocation rate through the nanopore is enzymatically controlled;
>
> [c] measuring an electrical signal which has a value that varies for at least N monomeric units of the template nucleic acid in the nanopore, wherein the measuring is performed as a function of time while the template nucleic acid translocates through the nanopore, wherein N is three or greater; and
>
> [d] determining the sequence of the template nucleic acid using the measured electrical signal from step (c) by performing a process including comparing the electrical signal from step (c) to calibration information that accounts for the electrical signal for 4 to the N sequence combinations.

75. Use of Defendants' products leads to direct infringement of this claim in at least the following way. First, Defendants' products include a nucleic acid sequencing instrument having an array of nanopores in contact with a solution containing sample template nucleic acids

(step a). A voltage is applied across the nanopores, which translocates the nucleic acid through the nanopore. This translocation is controlled via an enzyme (step b). Defendants' products then measure the electrical signal as a function of time of N monomeric units (where N is three or greater) of the template nucleic acid as they are translocated through the nanopore (step c). Lastly, the sequence of the template nucleic acid is determined using the measured electrical signal by comparing the electrical signal to calibration information that accounts for 4 to the N sequence combinations (step d).

76. On information and belief, Defendants have monitored PacBio's patent filings and has been aware of the '323 patent since its issuance on September 26, 2017. At a minimum, Defendants have had knowledge of and notice of its infringement since at least, and through, the filing and service of PacBio's complaint in this action and despite this knowledge continue to commit the aforementioned infringing acts.

77. Defendants actively, knowingly, and intentionally have induced, or have threatened to induce, infringement of at least claim 1 of the '323 patent through a range of activities. First, on information and belief, Defendants have induced infringement by controlling the design and manufacture of, offering for sale, and selling the Accused Products with the knowledge and specific intent that their customers will use the Accused Products to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants have admitted in an ongoing International Trade Commission investigation that it imports, sold for importation, and or/sells their MinION product and PromethION product within the United States. *See* Exhibit 10 ¶ 53.

78. Second, on information and belief, Defendants have induced infringement by their customers through the dissemination of promotional and marketing materials relating to the

Accused Products with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants promote the Accused Products on their website, stating that their products offer numerous benefits such as real-time DNA/RNA sequencing, no capital cost, long reads, scalability, high-fidelity, and rapid library preparation time. *See* Exhibit 11.

79. Third, on information and belief, Defendants have induced infringement by their customers through the creation of distribution channels for the MinION and/or GridION instruments in the United States with the knowledge and specific intent that their customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Defendants' website allows customers in the United States to purchase starter packs of Defendants' MinION and GridION X5 instruments that, when used, will lead to infringement of the '323 patent. As Defendants' website states, "[b]uy a Starter Pack to join the growing numbers in the Nanopore Community." *See* Exhibit 12. As another example, Defendants have created an early access program for their PromethION instrument that provides access to a PromethION device, site installation support, flow cells and reagents, and further information and support. *See* Exhibit 13. As another example, Defendants' website allows potential customers in the United States to register their interest in Defendants' SmidgION instrument, so that they can "be one of the first to start using SmidgION." Exhibit 14. Most recently, Defendants have announced that it "plan[s] to release Flongle into early access followed by release to general users within 2018." Exhibit 36.

80. Fourth, on information and belief, Defendants have induced infringement through the distribution of other instructional materials, product manuals, and technical materials with the knowledge and the specific intent to encourage and facilitate their customer's infringing (either literally or under the doctrine of equivalents) use of the Accused Products. Defendants are liable for their induced infringement of the '323 patent pursuant to 35 U.S.C. § 271 (b).

81. Defendants have contributed to, or have threatened to contribute to, the infringement by their customers of the '323 patent by, without authority, selling and offering to sell within the United States materials and apparatuses for practicing the claimed invention of the '323 patent, including, at least, the Accused Products. When, for example, any of the Accused Products is used by Defendants' customers for nucleic acid sequencing, the claimed method of the '323 patent for sequencing a nucleic acid template is performed, thereby infringing, literally or under the doctrine of equivalents, at least claim 1 of the '323 patent.

82. On information and belief, Defendants know that the Accused Products each constitute a material part of the inventions of the '323 patent and that they are not a staple article or commodity of commerce suitable for substantial noninfringing use. As documented above, the Accused Products consist of specialized substrates containing protein nanopores that are used in conjunction with specialized reagents for the purpose of sequencing nucleic acid templates. *See supra* ¶¶ 21-37. As such, none of the Accused Products nor any of the reagent kits for use with the Accused Products is a staple article of commerce suitable for substantial non-infringing use. Defendants know that the Accused Products are not staple articles or commodities of commerce suitable for substantial non-infringing use because the Accused Products have no use apart from infringing the '323 patent. Defendants are liable for their contributory infringement of the '323 patent pursuant to 35 U.S.C. § 271(c).

83. Defendants' infringement of the '323 patent has injured PacBio in their business and property rights. PacBio is entitled to recover monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial. Defendants' infringement of the '323 patent has caused irreparable harm to PacBio and will continue to cause such harm unless and until Defendants' infringing activities are enjoined by this Court.

PRAYER FOR RELIEF

WHEREFORE, PacBio prays for relief as follows:

A. Judgment that Defendants have infringed the '056 patent, the '929 patent, and the '323 patent;

B. An order permanently enjoining Defendants from further infringement of the '056 patent, the '929 patent, and the '323 patent;

C. An award of damages pursuant to 35 U.S.C. § 284 plus pre-judgment and post-judgment interest;

D. An award to PacBio of its costs and reasonable expenses to the fullest extent permitted by law;

E. A declaration that this case is exceptional pursuant to 35 U.S.C. § 285, and an award of attorneys' fees and costs; and

F. An award of such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38(b), PacBio hereby demands a trial by jury on all issues so triable.

Dated: August 23, 2018

Respectfully submitted,

FARNAN LLP

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