

Paper No. \_\_\_\_  
Filed: June 14, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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DROPWORKS, INC.,  
Petitioner,

v.

THE UNIVERSITY OF CHICAGO,  
Patent Owner.

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Case No. IPR2021-00100  
Patent No. 8,304,193

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**PETITIONER'S REQUEST FOR REHEARING  
PURSUANT TO 37 C.F.R. § 42.71**

## TABLE OF CONTENTS

I.	PRECISE RELIEF REQUESTED AND OVERVIEW .....	1
II.	LEGAL STANDARD .....	1
III.	ARGUMENT .....	2
	A. The Petition’s Citation To Quake Consistent With Other Office Decisions Does Not Immunize The ’193 Patent From IPR. ....	3
	B. The Decision Overlooked The Materiality Of New References.....	4
	C. Dropworks Addressed 10X’s IPR Petition and Reexamination. ....	11
IV.	CONCLUSION.....	13

## **I. PRECISE RELIEF REQUESTED AND OVERVIEW**

Petitioner Dropworks, Inc. respectfully asks the Board to reconsider the May 14, 2021 decision (Paper 9, “Decision”) denying institution of trial of claims 1-9, and 11 of U.S. Patent No. 8,304,193.

The Decision focused on whether Petitioner had sufficiently demonstrated error in the Board’s analysis of Quake. But Petitioner did not contend that the Board previously erred in its analysis of Quake. To the contrary, the Petition acknowledged gaps in the prior 10X challenges involving Quake and presented multiple new references (Litborn, Holliger, Schneegaß) never previously considered and materially different than what was before the Office. This new art and argument does not suffer from the deficiencies the Board had identified previously and is materially different. The basis for the Petition is therefore not that the Board erred on the record previously before it. Instead, the basis for the Petition is that the Office was previously presented with a materially incomplete record. This Petition presents a materially different record with new art and argument that does not suffer from the same deficiencies that the Board had identified previously. Accordingly, institution should be granted.

## **II. LEGAL STANDARD**

A decision whether to institute is reviewed for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion occurs when a decision was “based on an

erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors.” *General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, at 5 (Sept. 6, 2017) (precedential).

Congress authorized, but did not require, the Director to reject a petition “because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. §325(d). Section 325(d) does not apply where the prior Office proceeding “overlook[ed] specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.” *Advanced Bionics, LLC v. Med-El Elektro. Geräte GmbH*, IPR2019-01469, Paper 6 at 8 & n.9 (PTAB Feb. 13, 2020) (precedential). Nor should institution be denied under §325(d) where the Petition presents a new reference that is material to patentability even if a “majority of references cited in the Petition were analyzed during prosecution.” *Oticon Medial AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15, at 19-20 (Oct. 16, 2019) (precedential). The Board’s §325(d) analysis considers at least six factors. *Id.* at 9-10 & n.10 (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (prec. §III.C.5, ¶1).

### **III. ARGUMENT**

The Petition presented three new references that were never previously considered by the Office and demonstrated that these references contained disclosure

material to patentability that was not previously before the Office. The Decision reflects an abuse of discretion insofar as it required Petitioner to prove that the Office had erred regarding Quake’s teachings when the Petition *embraced* the Office’s findings regarding Quake. The Decision overlooked that each of Litborn, Schneegaß, and Holliger plainly and expressly disclose PCR in sub-microliter droplets substantially surrounded by oil (and report actual reduction to practice)—content absent from the prior Kopp and Haff references considered previously. The Decision thus failed to apply the *Becton, Dickinson* factors consistent with §325(d).

**A. The Petition’s Citation To Quake Consistent With Other Office Decisions Does Not Immunize The ’193 Patent From IPR.**

The Petition relied on Quake for claim elements the Office had already concluded are disclosed in it. In that circumstance, the fact that the reference was previously considered is not an appropriate reason to deny institution. *See Qualcomm Inc. v. Monterey Research, LLC*, IPR2021-00120, Paper 17, at 19 (Jun. 8, 2021) (“[I]t appears that all parties agree that Chien discloses using spacers as an etch mask....Thus, although Chien itself was previously presented to the Office, the combinations asserted in the Petition that include Chien were not previously presented.”).

Petitioner is not asking the Office to revisit a prior determination about Quake. Both Petitioner and the Office have acknowledged Quake’s teachings as uncontroversial. *See, e.g.*, Decision at 11 (acknowledging Quake “disclosed all claim

elements except conditions suitable for an autocatalytic reaction, similar to the grounds advanced in the present Petition”), 14-15 (acknowledging “the Examiner’s correct statement regarding the disclosure of Quake”); *Dropworks, Inc. v. Lawrence Livermore Nat’l Sec. LLC.*, IPR2021-00218, Paper 15, at 23-25, 31-33, 35 (Jun. 1, 2021); *Dropworks, Inc. v. Lawrence Livermore Nat’l Sec. LLC.*, IPR2021-00302, Paper 17, at 23-24, 32-34, 36 (Jun. 2, 2021).

Although Quake itself was previously presented, the additional art that fills in the gaps in Quake’s disclosure were not previously presented. The Decision nonetheless dissected each ground and focused on whether “the prior proceedings before the Office involved Quake” and whether Quake “is central to every ground[.]” Decision at 9-11; *see also* Decision at 19 (“All of these proceedings focused heavily on Quake”), 11 (Quake was not “simply a peripheral or secondary reference in the prior proceedings”). The Decision overlooked that whether a reference was primary or secondary does not control the §325(d) analysis. *NuVasive, Inc. v. Acantha LLC*, IPR2020-00706, Paper 11, at 27 (Aug. 25, 2020) (“*Advanced Bionics* does not draw any distinction of primary or secondary references”).

#### **B. The Decision Overlooked The Materiality Of New References.**

The prior 10X challenges to the ’193 Patent relied on Haff and Kopp in addition to Quake. Neither reference disclosed sub-microliter droplets substantially surrounded by oil. Haff’s PCR reaction volume was too large (mL-scale) such that

the reference lacked sub-microliter droplets entirely. Pet. 8-9; *see also* Pet. 14, 73. Kopp's PCR reaction volume was small enough but had no water-oil interface at all. Pet. 10, 15; EX1011, 1047; EX1028, 5902, 7743. In contrast, the present Petition submits three never previously considered references, each of which discloses sub-microliter droplets substantially surrounded by oil. Pet. 2, 19, 27, 39, 55, 57-58, 71-72, 73-75. Moreover, each reference reports *actual reduction to practice* of PCR in those droplets. *Id.* These disclosures were absent from Haff and Kopp.

Holliger discloses sub-microliter w/o droplets substantially surrounded by oil and reports successful PCR in those droplets. This is disclosed plainly in the reference and is beyond dispute. For example, Holliger disclosed *aqueous compartments* in the water-in-oil emulsion having average dimensions less than 2 picoliters in size. Pet. 30. Holliger also reports successfully performing PCR amplification in sub-microliter w/o droplets. Pet. 37-41; EX1006, 52:25-53:2 (PCR "proceeded efficiently within the compartments of this water-in-oil composition"); EX1006, 47:16-24, Fig. 2 (Holliger's "entire aqueous phase containing the biochemical components is compartmentalized in **discrete droplets**"). Holliger thus demonstrates that a sub-microliter compartment that is even completely surrounded with the same type of oils used in Quake provided conditions suitable for PCR.

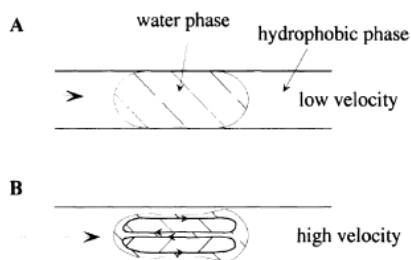
The Decision says that "Holliger performs its PCR method in an emulsion containing millions of various-sized vesicles" Decision at 13. But that does not

change the fact that Holliger discloses successful PCR in sub-microliter w/o droplets substantially surrounded by the same oils used in Quake. Nothing in the POPR or Decision demonstrates otherwise. Pre-Institution Reply at 3-4 (explaining that even if PCR was successful only in the larger droplets depicted in the emulsion of Holliger Fig. 2, these droplets are still well-within the sub-microliter range envisioned by the patent); *Dropworks, Inc.*, IPR2021-00218, Paper 15, at 33-38 (rejecting argument that the “broad distribution of droplet sizes characteristic of bulk emulsions” allegedly created in Holliger undermined reasonable expectation of success for performing PCR in Quake’s droplets); *Dropworks, Inc.*, IPR2021-00302, Paper 17, at 23-24, 33-39 (same).

The Decision comments that Holliger’s actual reduction to practice of PCR in w/o droplets did not specifically occur in “a microfluidic system.” Decision at 19. But the point is that Holliger showed an actual reduction to practice of PCR in sub-microliter w/o droplets and for that reason Holliger is materially different from Kopp or Haff. Patent Owner previously argued that the water-oil interface in sub-microliter droplets would preclude PCR. Holliger demonstrates that Patent Owner was wrong.

Each of Litborn and Schneegaß also discloses sub-microliter w/o droplets substantially surrounded by oil and reports successful PCR in those droplets—actual reduction to practice. Each of these references expressly discloses forming the w/o PCR droplets in a microfluidic systems using continuous flow. Litborn, for example,

discloses that “We have carried out preliminary experiments with *a flow based PCR reaction*, where the reaction mixture is interspaced with a hydrocarbon, as described above. Amplification was successful.” EX1007, 453 (emphasis added); Pet. 60. Litborn’s reference to “the reaction mixture [being] interspaced with a hydrocarbon, as described above,” refers to Fig. 7 and its accompanying description. EX1007, 452-53.



**Figure 7:** A: Transport of a water droplet in a hydrophobic solvent at low velocity. B: Same as in A, but at a high velocity.

Regarding interspacing PCR mixture with hydrocarbons, Litborn explains that when “two immiscible fluids” are used for “sequential flow reactions,” “the droplet of water” in a continuous flow of hydrocarbon in a hydrophobized channel “detaches from the surface while the hydrocarbon creates a layer between the channel surface and droplet (Figure 7).” EX1007, 452-53 (“Thus, there is no more surface contact of the water (and no more risk for surface interactions.”). Litborn unambiguously discloses successful PCR amplification in sub-microliter w/o droplets using standard hydrocarbon. Pet. 20, 63-64, 72. Neither Kopp or Haff contains such a disclosure, and therefore Litborn is also materially different from the art that was previously

considered.

Schneegaß confirmed that successful PCR in w/o droplets formed in standard hydrocarbons was known, and also that it had been repeated experimentally (*i.e.*, actual reduction to practice). Schneegaß formed the PCR droplets in mineral oil on a microfluidic chip, and Schneegaß used Tween 20 in the PCR mixture to “stabilize the droplets.” *See, e.g.*, Pet. 21-22; EX1009, 109-10; *see also Dropworks, Inc.*, IPR2021-00218, Paper 15, at 37-38 (rejecting argument that a POSA lacked a reasonable expectation of success for performing PCR in Quake’s droplets based on Schneegaß); *Dropworks, Inc.*, IPR2021-00302, Paper 17 (same). The Petition thus demonstrated that Schneegaß unambiguously discloses successful PCR amplification in sub-microliter w/o droplets using standard hydrocarbon. Pet. 21-22, 26, 57, 72. Schneegaß’s disclosure is not found in Kopp or Haff. Schneegaß therefore contains materially different content.

Finally, Patent Owner submitted the Curcio reference (EX2003) with its preliminary response. Curcio successfully performed PCR amplification in decane as well as in fluorinated oil. Pre-Inst. Reply at 3-4; EX2003, Abstract, 4-5 & Figs. 2-3. After the Petition was filed, Patent Owner (with Bio-Rad as exclusive licensee) conceded that the ’193 Patent is not entitled to the priority date of its provisional, making Curcio prior art to the presently challenged claims. *See Dropworks, Inc.*, IPR2021-00218, Paper 15, at 2-3, 13-14, 17-21; *Dropworks, Inc.*, IPR2021-00302,

Paper 17 (same). Curcio thus further confirms that the newly-asserted references are materially different than Haff and Kopp.

The Decision's only justification for ignoring the materially different disclosure of Litborn and Schneegaß is that they are allegedly "substantially similar" to Haff and Kopp because they all "disclose segmented-flow systems." Decision at 13, 16-18. First, what matters is not just perceived similarities among the references but their salient differences: Litborn and Schneegaß disclose PCR in sub-microliter aqueous droplets substantially surrounded by oil, whereas Haff and Kopp do not. *See NuVasive, Inc.*, IPR2020-00706, Paper 11, at 21 (Aug. 25, 2020) (even many similarities between newly-asserted and previously-considered references "does not demonstrate that there are no material differences").

Second, the Decision fails to explain how, even if true, a "segmented-flow system" necessarily excludes or is mutually-exclusive with w/o droplet PCR. And, in any event, the premise for the assertion is incorrect. The Decision states that Litborn and Schneegaß "reasonably can be interpreted to pertain primarily to segmented flow systems where the aqueous phase is not substantially surrounded by the carrier fluid." Decision at 18-19. The Decision's sole explanation for this statement was that "Litborn Figure 6B shows a 'droplet' having significant contact between aqueous phase and channel wall, and discusses conducting PCR only in system where samples are 'interspaced' with hydrocarbon." *Id.* But the Decision's

focus on Fig. 6B overlooks Litborn's disclosures about w/o droplet PCR in relation to **Fig. 7** that was relied on in the petition. *Compare, e.g.*, EX1007, 452 (Fig. 6 depicts "sample plugs, interspaced by air (or gas)") *with* Fig. 7 ("Transport of a water droplet in a hydrophobic solvent").

Beyond citing the wrong disclosure of Litborn, the Decision's assertion that the droplet in Fig. 6B appears to have "significant contact between aqueous phase and channel wall" overlooked the '193 Patent's disclosure that the patent's droplets also visually depict significant contact between aqueous phase and channel wall. *See, e.g.*, Pet. 6 (showing patent's depiction of plugs that appear to have significant contact with the channel wall); EX1001, Figs. 3, 12, 27. The Board also previously rejected the argument that "substantially surrounded" in the claims means carrier fluid necessarily wets the walls of the channels or separates droplets from the channel surface. EX1027, 7-8 (listing carrier fluid wetting the channel walls to separates the plug from the walls as among "optional characteristics" that are "preferabl[e]" but not required by the claims). The Decision's requirement that prior art w/o droplets lack any significant contact with the channel wall at all times is not commensurate with the patent or the Board's own prior interpretation of the patent.

The Decision also overlooked that the Petition cited Holliger and Schneegaß to support motivation to combine and reasonable expectation of success for the Quake/Litborn ground (and vice versa). *See, e.g.*, Pet. 55-58. Moreover, Petitioner

provided evidence and expert testimony explaining that, *inter alia*, forming the droplets at the junction as disclosed in Quake would beneficially produce monodisperse (uniformly sized) PCR droplets with reduced cross-talk and high-throughput. Pet. 25-26, 56-57. That Litborn, Schneegaß, and Curcio successfully performed PCR amplification in sub-microliter w/o droplets regardless of whether there was any initial contact with the channel walls during segment loading (prior to droplet formation) only indicates that PCR amplification would work even better using the proposed combination. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (nonobviousness cannot be established by attacking the references individually where the rejection is based upon the teachings of a combination of references). Such evidence and argument is materially different than what was presented to the Office previously.

### **C. Dropworks Addressed 10X's IPR Petition and Reexamination.**

Patent Owner avoided cancellation of the challenged claims during the reexamination based on unsupported argument that using standard hydrocarbon oil would preclude PCR by destroying proteins. *See, e.g.*, Pet. 2, 8-10, 74-75; EX1028, 5899 (“traditional hydrocarbons, such as decane...and mineral oil...are not remotely biocompatible and will destroy proteins.”). Neither the Board nor either examiner previously considered *any* reference that reported successful PCR in a sub-microliter reaction volume having a mineral oil- or standard hydrocarbon-water interface, as

the newly cited references did. *See, e.g.*, Pet. 2, 19, 27, 39, 55, 57-58, 71-72, 73-75. Haff's PCR reaction volume was large (mL-scale), not sub-microliter volumes. Pet. 8-9; *see also* Pet. 14, 73. Kopp's PCR reaction volume was small but had no water-oil interface at all. Pet. 10, 15; EX1011, 1047; EX1028, 5902 ("Kopp does not even use a carrier fluid that is immiscible with a reagent fluid"), 7743 ("Kopp is silent with respect to oil as a carrier fluid"). Dropworks's IPR petition, in contrast, provided new and materially different evidence (*e.g.*, Holliger, Litborn, and Schneegaß) disclosing that mineral oil- and standard hydrocarbon-water interfaces in sub-microliter reaction volumes provided conditions suitable for PCR.<sup>1</sup> Had Dropworks's Petition argument and evidence been before the examiner, the claims would not have been confirmed. Pet. 71-75.

The Board denied 10X's IPR petition in IPR2015-01163 because of the failure of **10X's petition** to address reasonable expectation of success. Pet. 9; EX1027, 15

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<sup>1</sup> Moreover, the Petition also cites to Shaw Stewart's disclosure as demonstrating that fluorinated hydrocarbons are suitable carrier fluids for droplets containing biological materials for biological or chemical assays. Pet. 53-54, 70-73. As such, Shaw Stewart further demonstrates error by the Examiner in crediting Patent Owner's manufactured argument.

(identifying “the lack of any reasoned explanation in the Petition for why this combination would have been successful”), 16 (“conclusory statement”). Petitioner also remedied these deficiencies as well. *See, e.g.*, Pet. 2, 8-10, 74-75. The present Petition addresses reasonable expectation of success in detail (*e.g.*, Pet. 13-17, 22-27, 53-54, 54-58, 70-71, 71-75; EX1002, ¶¶161-66, 169-174, 225-29, 232-34, 240-43, 289-93, 295-302) and, therefore is materially different from the 10X petition case. *See, e.g., Alphatec Holdings, Inc. v. NuVasive, Inc.*, IPR2019-00546, Paper 17, at 10 (Jul. 9, 2019) (Board considers patent owner litigation tactics and is reluctant to prejudice a subsequent petitioner due to the deficiencies of a previous petitioner).

Given the deficient showings in the prior proceedings, it was an abuse of discretion to deny institution under §325(d) and prejudice Dropworks due to the shortcomings in a challenge by an unrelated party. *See* Nov. 2019 Consolidated Trial Practice Guide at 62 (Board must balance “petitioner’s desire to be heard” in making §325(d) evaluation). The asserted combination of references is unlike any combination of references previously considered by the Office and demonstrates that the claims of the ’193 Patent are invalid.

#### **IV. CONCLUSION**

For the reasons set forth above and in the Petition and petitioner’s reply, Petitioner respectfully requests rehearing and institution of *inter partes* review.

Respectfully submitted,

Date: June 14, 2021

/ Michael T. Rosato /

Michael T. Rosato, Lead Counsel

Reg. No. 52,182

## **CERTIFICATE OF SERVICE**

I certify that the foregoing Petitioner's Request for Rehearing Pursuant to 37 C.F.R. § 42.71 was served on this 14th day of June, 2021, on the Patent Owner at the following electronic service addresses:

Derek Walter  
Robert Magee  
Sutton Ansley  
WEIL, GOTSHAL & MANGES  
[derek.walter@weil.com](mailto:derek.walter@weil.com)  
[robert.magee@weil.com](mailto:robert.magee@weil.com)  
[sutton.ansley@weil.com](mailto:sutton.ansley@weil.com)  
[Bio-Rad.Dropworks@weil.com](mailto:Bio-Rad.Dropworks@weil.com)

Respectfully submitted,

Date: June 14, 2021

/ Michael T. Rosato /  
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Michael T. Rosato, Lead Counsel  
Reg. No. 52,182