Paper: 10 Entered: October 24, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SWEEGEN, INC., Petitioner,

v.

PURECIRCLE USA INC. AND PURECIRCLE SDN BHD, Patent Owners.

IPR2019-01017 Patent 9,243,273 B2

Before SUSAN L. C. MITCHELL, JO-ANNE M. KOKOSKI, and JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, Administrative Patent Judge.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Sweegen, Inc. ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1–14 of U.S. Patent No. 9,243,273 B2 (Ex. 1001, "the '273 patent"). PureCircle USA Inc. and PureCircle SDN BHD (collectively, "Patent Owners") filed a Preliminary Response (Paper 7, "Prelim. Resp.").

Under 35 U.S.C. § 314(a), the Board "may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons explained below, upon consideration of the Petition, Preliminary Response, and the evidence of record, we determine that the information presented in the Petition does not show that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. Accordingly, we do not institute an *inter partes* review.

A. Related Proceedings

The parties indicate that the '273 patent is the subject of *PureCircle USA Inc. and PureCircle Sdn Bhd v. SweeGen, Inc. and Phyto Tech Corp d/b/a Blue California*, Case No. 8:18-cv-1679 JVS (C.D. Cal.). Pet. 72; Paper 5, 2.

B. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–14 of the '273 patent are unpatentable in view of the following grounds:

Claims Challenged	Statutory Basis	Reference(s)
1–14	§ 103	Ohta, ¹ WO378 ²
1–14	§ 103	WO227 ³
1–6, 12–14	§ 102	WO227

Petitioner relies on the Declaration of D. Eric Walters, Ph.D. (Ex. 1003) in support of its contentions. Patent Owner relies on the Declarations of Professor Joe P. Foley (Ex. 2001), Professor Robert Michael Williams (Ex. 2002), and Avetik Markosyan (Ex. 2003) in support of its Preliminary Response.

C. The '273 Patent

The '273 patent is directed to biocatalytic methods for preparing steviol glycosides from other steviol glycosides. Ex. 1001, 4:17–20. Steviol glycosides are a class of compounds found in the leaves of the *Stevia rebaudiana* Bertoni plant. *Id.* at 1:38–40. Purified steviol glycosides can be used in consumable products as non-caloric sweeteners. *Id.* at code (57), 3:36–37.

The '273 patent discloses the conversion of Rebaudioside D ("Reb D") to Rebaudioside X ("Reb X") by contacting Reb D with a UDP-glycosyltransferase ("UGT") enzyme, such as UGT76G1, which catalyzes the reaction of UDP-glucose and Reb D to produce Reb X. Ex. 1001, 12:58–61, 13:2–3. As shown in the figure below, Reb D is converted to Reb

⁻

¹ Ohta, Masaya et al., Characterization of Novel Steviol Glycosides from Leaves of *Stevia rebaudiana* Morita, Journal of Appl. Glycosci., Vol. 57, No. 3, 199–209 (2010) (Ex. 1004, "Ohta").

² Kishore et al., WO 2011/153378 A1, published December 8, 2011(Ex. 1005, "WO378").

³ Mikkelsen et al., WO 2014/122227 A2, published August 14, 2014 (Ex. 1009, "WO227").

X through the addition of a glucose unit to the disaccharide at the C19 position of Reb D. *Id.* at 12:61–62, Fig. 2. A portion of Figure 2 from the '273 patent, which shows this reaction, is reproduced below:

Figure 2 above shows the conversion of Reb D to Reb X.

Examples 1, 2, and 7–12 of the '273 patent describe the *in vivo* and *in vitro* production of UGT76G1. Ex. 1001, 20:23–21:50, 23:48–26:21. Examples 6 and 14 of the '273 patent describe catalytic reactions of Reb D to Reb X using *in-vitro* produced UGT76G1. *Id.* at 23:26–46, 26:5–27:11. The '273 patent also describes the use of high-performance liquid chromatography ("HPLC") to separate the components of the reaction mixture of Example 14 and the use of nuclear magnetic resonance ("NMR") and high resolution mass spectrometry ("HRMS") to describe the structure of the reaction components. *Id.* at 27:3–11, 29:17–32:28.

D. Illustrative Claim

Petitioner challenges claims 1–14 of the '273 patent. Claim 1, which is the only independent claim of the '273 patent, is illustrative of the challenged claims, and is reproduced below:

1. A method for making Rebaudioside X comprising a step of converting Rebaudioside D to Rebaudioside X using a UDP-glucosyltransferase, wherein the conversion of Rebaudioside D to Rebaudioside X is at least about 50% complete.

Ex. 1001, 35:2–5. Challenged claims 2–14 depend, directly or indirectly, from claim 1.

II. ANALYSIS

A. Principles of Law

"In an [inter partes review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)) (requiring inter partes review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in inter partes review).

To show anticipation under § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims in order to find anticipation. *See In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). It is also permissible to take into account not only the literal teachings of the prior art reference, but also the inferences an ordinarily skilled person would draw from the reference. *See Eli Lilly & Co. v. L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *see also In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

Turning to obviousness, a claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). "An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." CRFD Research, Inc. v. Matal, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)). A conclusion of obviousness "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR, 550 U.S. at 418 (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)).

B. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner, relying on the testimony of Dr. Walters (Ex. 1003), contends that a person of ordinary skill in the art as of the relevant date would have been a person with:

a bachelor's degree, master's degree or Ph.D. in chemistry, biochemistry, molecular biology, chemical engineering, genetic engineering, or a related field and having at least five years of experience researching and developing methods for enzyme expression in recombinant microorganisms, including bacterial and yeast. The person would have familiarity with modifying naturally occurring nucleic acid sequences expressing one or more enzyme(s) of interest to optimize their expression in the recombinant microorganism. The person would also have familiarity with using such recombinant enzymes as catalysts for biotransformation of organic compounds, such as steviol glycosides, and subsequent purification of the resulting products to produce food additives, such as artificial sweeteners (including but not limited to rebaudiosides).

Pet. 34–35 (citing Ex. $1003 \, \P \, 73$) (citations omitted).

Patent Owners dispute Petitioner's description of the level of ordinary skill in the art and contend that both Patent Owners' Declarant (Dr. Williams), and Petitioner's Declarant in the underlying litigation (Dr. Webb), assert that Petitioner's definition requires too high a level of ordinary skill. Prelim. Resp. 59. According to Patent Owners, Dr. Webb opines that the following qualifications are unnecessary for a person of ordinary skill in the art: "(1) several years of experience researching and developing methods for enzyme expression in recombinant organisms;" "(2) familiarity with using recombinant enzymes as catalysts for biotransformation of organic compounds such as steviol glycosides;" and "(3) experience with subsequent purification of the products." *Id.* (citing Ex. 2016, 173:7–23; 174:23–175:14). Patent Owners, with supporting testimony from Dr. Williams (Ex. 2002), contend that "[a] person of ordinary skill in the area of process chemistry at the time of the '273 Patent's invention would have had a Ph.D. in chemistry, biotechnology, biochemistry, or molecular biology including practical laboratory experience in chemical

process manufacturing involving the use of enzymes gained during these Ph.D. studies." *Id.* at 59-60 (citing Ex. $2002 \, \P \, 151$).

We find that a person of ordinary skill in the art would have had an advanced degree in chemistry, biotechnology, biochemistry, or molecular biology, and research experience and knowledge of recombinant techniques and chemical process manufacturing involving the use of enzymes. This definition is consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Although we do not fully adopt either party's definition of a person of ordinary skill in the art, our determination regarding Petitioner's challenge does not turn on the differences between Petitioner's and Patent Owners' definitions, and we note that our conclusions would be the same under either definition.

C. Claim Construction

Because this *inter partes* review is based on a petition filed after November 13, 2018,⁴ claim terms are construed using the same claim construction standard that would be used to construe the claim in a civil

⁴ On October 11, 2018, the USPTO revised its rules to harmonize the Board's claim construction standard with that used in civil actions under 35 U.S.C. § 282(b) in federal district courts. Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (now codified at 37 C.F.R. pt. 42 (2019)). This rule change applies to petitions filed on or after November 13, 2018.

action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b). Under this claim construction standard, claim terms are given their ordinary and customary meaning as would have been understood by one of ordinary skill in the art at the time of the invention. *See id.*; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). A patentee may define a claim term in a manner that differs from its ordinary and customary meaning; however, any special definitions must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Although neither party expressly proposes an express claim construction of any claim term, there does appear to be disagreement as to the meaning of the "at least about 50% complete" limitation in claim 1 from the parties' discussions of whether this limitation is taught in the asserted art. Pet. 67–71; Prelim. Resp. 23–28. Upon review of the parties' arguments and the evidence of record, however, we determine that none of the claim terms require express construction for purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.")).

D. Asserted Obviousness of Claims 1–14 over Ohta in View of WO378
 Petitioner contends that claims 1–14 would have been obvious over
 the combined disclosures of Ohta and WO378. Pet. 49–62. Patent Owners
 dispute Petitioner's contentions. Prelim. Resp. 31–51.

1. Ohta

Ohta describes the characterization of steviol glycosides extracted from the leaves of the *Stevia rebaudiana* Morita plant. Ex. 1004, 1.⁵ The *S. rebaudiana* Morita plant was developed by selective breeding from *S. rebaudiana* Bertoni, in order to produce an extremely high ratio of rebaudioside A. *Id.* Ohta characterizes the structures of 21 steviol glycosides, including Reb M (also known as Reb X), by using electrospray ionization mass spectrometry/mass spectrometry ("ESI-MS/MS"), ¹H- and ¹³C-NMR, and/or chemical analyses after separation by HPLC. *Id.* at 1, 6, Table 4. Ohta also provides the relative percentages of the different steviol glycosides in the leaves of the *S. rebaudiana* Morita and *S. rebaudiana* Bertoni plants. *Id.* at 6, Table 4.

2. WO378

WO378 describes the recombinant production of steviol glycosides by recombinant hosts and describes experiments in which recombinant UGTs are used to catalyze glycosylation of different steviol glycosides. Ex. 1005, 2:9–12, 67:6–109:13.⁶ According to WO378, the produced steviol glycoside can be selected from the group consisting of "steviol-13-O-glucoside, steviol-19-O-glucoside, rubusoside, rebaudioside A, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside E, rebaudioside F, and dulcoside A." *Id.* at 7:8–10.

⁵ The cited page numbers in Ex. 1004 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

⁶ The cited page numbers in Ex. 1005 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

3. Analysis

Petitioner asserts that a person of ordinary skill in the art "would have been motivated to make reb X because it was known to have desirable properties for use as a high-potency, non-nutritive sweetener." Pet. 49 (citing Ex. 1003 ¶ 34). In support of this contention, Petitioner cites to Ohta, which states that "glycosylation at both C13 (R_2) and C19 (R_1) of steviol are essential for sweetness" and that "sweetness intensity of steviol glycosides was increased by extending the ester sugar chain at the C19 position (R_1) ." Id. (citing Ex. 1004, 9). Petitioner also cites to Ohta's statement that SG17 (Reb X) "had a sweetness equivalent to rebaudioside A, and gave a slightly latent sweet sensation to some volunteers in our laboratory (data not shown)." *Id.* (citing Ex. 1004, 9). According to Petitioner, WO420⁷ provides further evidence that a person of ordinary skill in the art would have been motivated to make Reb X because WO420 reports that Reb X exhibited less bitter taste, less astringent taste, less licorice taste, less sweet aftertaste, and greater "quality of sweet taste" as compared to Reb D, and that these results "clearly show that Reb X possesses superior taste profile to already known steviol glycosides." *Id.* at 50 (citing Ex. 1024, 125).8

_

⁷ Prakash et al., WO 2013/096420 A1, published June 27, 2013 (Ex. 1024, "WO420").

⁸ Patent Owners assert that WO420 is not prior art under 35 U.S.C. § 102(e) because the '273 patent and WO420 were commonly owned by PureCircle and Coca-Cola at the time of the invention. Prelim. Resp. 38–40. Because we determine that Petitioner has not demonstrated a reasonable likelihood that claims 1–14 would have been obvious over the combined teachings of Ohta and WO337, regardless of whether WO420 is prior art, we do not need to decide the issue of whether WO420 is prior art to the '273 patent for the purposes of this Decision.

Petitioner further asserts that a person of ordinary skill in the art would have had a reasonable expectation of successfully converting Reb D to Reb X using a UGT enzyme because

a) it was known that UGTs expressed naturally in *Stevia rebaudiana* plants catalyze 1,3 addition of a glucose molecule to a C-19 position of reb D to form reb X; and b) it was known that UGT76G1 is expressed naturally in *Stevia rebaudiana* plant leaves and is highly active at catalyzing the 1,3 addition of a glucose molecule to steviol glycosides, which is the same reaction necessary to convert reb D to reb X.

Pet. 50–51. Petitioner contends that, according to Table 4 of Ohta, the relative proportion of SG18 (Reb D) in the *Stevia rebaudiana* leaves is 2.1% and the relative proportion of SG17 (Reb X) is 1%. *Id.* at 52 (citing Ex. 1004, 6). With supporting testimony from Dr. Walters, Petitioner asserts that a person of ordinary skill in the art "would understand that conversion of reb D to reb X in the plant was about 1(1+2.1) = 32.3% complete." *Id.* at 51-52 (citing Ex. 1004, 6, Table 4; Ex. 1003 ¶ 106). Petitioner contends that WO420 corroborates this calculation because it describes Reb X as being present in the *Stevia rebaudiana* Bertoni plant leaves at 0.10% and Reb D being present at 0.21%, which results in a conversion calculation of 0.1/(0.21+0.1) = 32.3%. *Id.* at 53 (citing Ex. 1024, 123; Ex. 1003 ¶ 107). Petitioner concludes that this informs a person of ordinary skill in the art that "UGTs expressed in the *Stevia rebaudiana* plant catalyze addition of a glucose molecule to a C-19 position of reb D to form reb X." *Id.* (citing Ex. 1003 ¶ 107).

Petitioner further asserts that WO378 discloses that UGT76G1 catalyzes 1,3-glucosylation reactions and, therefore, informs a person of ordinary skill in the art "that UGT76G1 is the enzyme in *Stevia rebaudiana* that catalyzes 1,3 addition of a glucose molecule to a C-19 position of reb D

to form reb X." Pet. 53–54 (citing Ex. 1005, 130–133; Ex. 1003 ¶ 109). According to Petitioner, WO378 also discloses that UGT76G1 is highly efficient at catalyzing 1,3-glucosylation because Figure 9 shows that "UGT76G1–catalyzed conversion of stevioside to reb A was 100% within the cell, which is where the UGT76G1 enzyme is made and therefore where there is maximum contact between the stevioside substrate and the UGT76G1 enzyme." *Id.* at 54–55 (citing Ex. 1005, 86–88, 141; Ex. 1003 ¶¶ 110–111).

According to Petitioner, one of ordinary skill in the art would have had a reasonable expectation of achieving at least about 50% conversion of Reb D to Reb X because increasing the conversion would have required only routine optimization. Pet. 56–58 (citing Ex. 1003 ¶¶ 118–119, 124). Petitioner asserts that, based on the disclosure of WO378, a person of ordinary skill in the art would have understood that, to maximize conversion of Reb D to Reb X, the reaction should be conducted in vitro to maintain contact between the enzyme and the reactants, and that "[d]oing repeated enzyme assays with varying concentrations of reactants and/or enzymes is a matter of routine in the art." Id. at 56 (citing Ex. 1003 ¶¶ 67, 118–120; Ex. 1023, 11; Ex. 1028, 122:6–126:12). Petitioner also asserts that WO378 supplies exemplary in vitro reaction conditions and that "[s]ubstituting reb D as the steviol glycoside substrate and then varying the concentrations and reaction temperature would be routine and would predictably result in an increased yield of reb X." *Id.* at 57 (citing Ex. 1003 ¶¶ 121, 131; Ex. 1005, 82:11–17).

Lastly, Petitioner asserts that there would be a reasonable expectation of successfully achieving at least about 50% conversion of Reb D to Reb X

because it was known that the conversion in the *Stevia rebaudiana* plant is around 30% complete and a person of ordinary skill in the art would reasonably expect to increase the conversion rate "by conducting the reaction under controlled conditions that were known to increase conversion, such as by using a cell-free in vitro reaction at specified concentrations and temperature." Pet. 57–58 (citing 1003 ¶ 124). In support of this argument, Petitioner asserts that conversion of stevioside to Reb A, which uses the same UGT76G1 enzyme, is around 30% in the Stevia rebaudiana Bertoni plant but Ohta increased the conversion to 87% using selective hybridization breeding, and WO378 and WO989⁹ further increased the conversion of stevioside to Reb A to nearly 100% using recombinant UGT76G1. Id. at 58 (citing Ex. 1003 ¶ 125; Ex. 1005 ¶ 86–88, 141; Ex. 1028, 127:11–16). Petitioner concludes that the person of ordinary skill in the art "would reasonably expect to successfully increase the naturally occurring 30% conversion of reb D to reb X as high as desired, including to at least about 50% using recombinant UGT76G1 and maintaining contact between the enzyme and the reb D substrate." *Id.* (citing Ex. 1003 ¶ 125).

In response, Patent Owners argue that "there was no motivation to combine Ohta, which disclosed that trace amounts of Rebaudioside [X] were found in a special cultivar, with WO378, which disclosed methods of making other rebaudiosides." Prelim. Resp. 31. According to Patent Owners, at the time of the invention, Reb X was not a compound of interest because Ohta showed that Reb X was only present in small amounts in the proprietary Morita cultivar and was not found in the natural Bertoni plant.

⁹ Houghton-Larsen et al., WO 2013/022989 A2, published February 14, 2013 (Ex. 1028, "WO989").

Id. at 31, 33 (citing Ex. 1004, 6 (showing 1.0% Reb X (referred to as Reb M) in Morita, but not detected in Bertoni); Ex. 2016, 57:13–58:12).

Patent Owners also assert that the disclosure in Ohta relied on by Petitioner would not have motivated one of skill in the art to pursue Reb X. Prelim. Resp. 33–36. Specifically, Ohta states that Reb X "had a sweetness equivalent to rebaudioside A, and gave a slightly *latent* sweet sensation to some volunteers in our laboratory." *Id.* at 33 (citing Ex. 1004, 9). Patent Owners contend that this statement does not motivate an interest to pursue Reb X because it describes Reb X as merely "equivalent" to Reb A, which, in the Morita cultivar, comprises 61.6% of the *Stevia* leaf (61.6 times more than Reb M), making it a more attractive option than Reb X. *Id.* at 34 (citing Ex. 2002 ¶ 121). Also, according to Patent Owners and their Declarant, Dr. Robert Michael Williams, Ohta's suggestion that Reb X has "latent sweetness" (e.g., delayed sweetness) is a negative characteristic because rapid onset sweetness (as in natural sugars) is preferred. *Id.* at 6, 34 (citing Ex. 2002 ¶ 41–42, 124).

Patent Owners further assert that Petitioner's calculated conversion rate of Reb D to Reb X as disclosed in Ohta is incorrect. Prelim. Resp. 43–47. With supporting testimony from Dr. Williams, Patent Owners contend that "unlike in the recombinant biocatalysis systems, the process in the plant is far more complicated, is reversible, and includes not only addition of glucose units, but also subtraction of glucose units (degradation), making a conversion impossible to calculate using simplistic methods." *Id.* at 43–44 (citing Ex. 2002 ¶¶ 75–79). According to Patent Owners, Petitioner's litigation Declarant, Dr. Webb, agrees that there is no easy way to calculate the conversion from Reb D to Reb X in the plant. *Id.* at 44–45 (citing

Ex. 2016, 54:22–25, 55:1–7, 59:3–9, 60:1–8). Patent Owners also contend that WO420 does not corroborate Petitioner's calculated conversion rate because, when the conversion method is applied to other rebaudiosodes disclosed in Ohta and WO420, there are discrepancies in the results (e.g., the steviolbioside to Reb B conversion would be 71.4% based on the amounts disclosed in Ohta versus a conversion rate of 16.7% based on the amounts disclosed in WO420). *Id.* at 45–46.

Patent Owners also assert that in May 2012, it was not obvious that UGTs would add glucose in a 1,3-configuration to the C-19 end of Reb D, and thus, there was no reasonable expectation of success. Prelim. Resp. 47– 51. According to Patent Owners, "the UDP-glucosyltransferases claimed in all claims, including UGT76G1 claimed in claim 14, were only known to add glucose in a 1,3-glucosylation at the C-13 position, and not at the C-19 position as is required for the conversion of Rebaudioside D to [X]." Id. at 47 (citing Ex. 1009 ¶ 386). In support of this contention, Patent Owners cite to WO227, which refers to the conversion from Reb D to Reb X as among the "[n]ewly discovered UGT76G1 reactions" and also points to WO378, which explains that "a particular UDP-glucosyltransferase can add glucose at the C-19 position, but not where there is 1,3-bound glucose at the C-13 position, as is the case with Rebaudioside D." *Id.* at 48 (citing Ex. 1009 ¶ 387; Ex. 1005, 24:1–10). Patent Owners, therefore, contend that as of the priority date, it was an "open question" as to whether the UDPglucosyltransferases would be efficient at the C-19 position and, thus, "there was no reasonable expectation of success that UDP glucosyltransferases would convert Rebaudioside D to [X] at high conversions (at least about

50%) when the '273 Patent application was filed in May 2012." *Id.* at 50 (citing Ex. 1009).

Lastly, with supporting testimony from Dr. Williams, Patent Owners assert that the Reb D to Reb M conversion "is an entirely different reaction from the reactions disclosed in WO378" and, thus, "cannot be an optimization" of that reaction. Prelim. Resp. 50–51 (citing Ex. 2002 ¶ 121). According to Patent Owners, the patented invention is also not an optimization of the plant process because it is unknown exactly what process the plant uses to make the trace amounts of Reb X; therefore, it would be difficult to optimize this inefficient process. *Id.* at 51 (citing Ex. 2002 ¶¶ 56–57, 121). By contrast, according to Patent Owners, the '273 patent inventors developed a genetically engineered enzyme using microorganisms. *Id.* (citing Ex. 2002 ¶ 121).

For the reasons explained below, upon consideration of the Petition, Preliminary Response, and the evidence of record, we are not persuaded that Petitioner and Dr. Walters have provided sufficient argument and supporting evidence to demonstrate a reasonable likelihood that challenged claims 1–14 would have been obvious over the combined teachings of Ohta and WO378.

First, Petitioner has not presented sufficient information to show that one of skill in the art would have been motivated to pursue Reb X from the disclosure in Ohta. Although Ohta discloses the presence of Reb X in the proprietary *Stevia rebaudiana* Morita plant, it is only present at a relative percentage of 1%, and was not detected in the Bertoni plant. Ex. 1004, 6, Table 4 (Reb X referred to as SG17 (reb M)). In addition, Petitioner points to the language in Ohta stating that Reb X "gave a slightly latent sweet sensation" as providing motivation to pursue Reb X; however, Patent

Owners, with supporting testimony from Dr. Williams, explain that latent (rather than rapid-onset) sweetness is a negative characteristic for rebaudioside sweeteners. Pet. 49 (citing Ex. 1004, 9); Prelim. Resp. 6, 34 (citing Ex. 2002 ¶ 41–42, 124).

Second, Petitioner has not presented sufficient information to show that there was a motivation to combine Ohta with WO378. In fact, Petitioner fails to explicitly mention any particular motivation to combine these two references. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) ("A party seeking to invalidate a patent on obviousness grounds must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.") (citations and internal quotations omitted).

In addition, Petitioner and Dr. Walters have not presented sufficient evidence that one of skill in the art would have had a reasonable expectation of success in converting Reb D to Reb X using UGTs at a conversion rate of at least 50%. We are not persuaded that Dr. Walter's calculated 32.3% conversion rate of Reb D to Reb X in the *Stevia rebaudiana* plant is correct (Pet. 52) because, according to Patent Owners' Declarant and Petitioner's Declarant in the corresponding litigation, the conversion process in the plant is too complicated for the simplistic calculation done by Dr. Walters.

Prelim. Resp. 43–47 (citing Ex. 2002 ¶¶ 75–79; Ex. 2016, 54:22–25, 55:1–7,

Petitioner also cites to WO420 as corroboration of the teachings of Ohta. Pet. 50. Although WO420 does appear to disclose a favorable taste profile of Reb X (including a faster sweetness onset), Petitioner still fails to present sufficient arguments as to why one of skill in the art would have been motivated to combine Ohta with WO378.

59:3–9, 60:1–8; Ex. 2024, 72:1–13). Furthermore, contrary to Petitioner's contention, WO420 does not appear to corroborate this calculated conversion rate. Pet. 53. Although using the same calculation technique resulted in a similar conversion percentage from Reb D to Reb X in Ohta and WO420, this was not the case when conversion percentages were calculated for other rebaudiosides (such as Steviolbioside to Reb B) disclosed in Ohta and WO420. Prelim. Resp. 45–46 (citing Ex. 2002 ¶ 78).

Furthermore, Petitioner fails to present persuasive evidence that it would have been obvious to one of ordinary skill in the art that UGTs would add glucose in a 1,3-configuration to the C-19 end of Reb D to catalyze conversion to Reb X. Petitioner cites to several figures in WO378 in support of its argument that WO378 informs a person of ordinary skill in the art that UGT76G1 catalyzes 1,3 addition of a glucose molecule to a C-19 position of Reb D to form Reb X; however, all of these examples show addition of a glucose at the C-13 position rather than the C-19 position. Pet. 53–54 (citing Ex. 1005, 130–133). Petitioner and Dr. Walters do not adequately explain why WO378's disclosure of the ability of UGT76G1 to catalyze the addition of a glucose at the C-13 position of a stevioside molecule would have suggested to one of ordinary skill in the art that they could expect this enzyme to catalyze the addition of a glucose at a different part of the molecule (i.e., the C-19 position) with at least about a 50% conversion rate.

We also are not persuaded by Petitioner's and Dr. Walters' argument that achieving at least about a 50% conversion of Reb D to Reb X would have required only routine experimentation and optimization. Pet. 56–57. In support of this argument, Petitioner cites to *in vitro* reaction conditions disclosed in WO378. Pet. 57 (citing Ex. 1005, 82:11–17). However, these

reaction conditions were disclosed for the testing of UGT polypeptides for 1,2-glycosylation activity, using steviol-13-O-monoglucoside as a substrate, and not for converting Reb D to Reb X. Ex. 1005, 82:11–12. Petitioner and Dr. Walters do not adequately explain why WO378's disclosure of these reaction conditions for a different reaction would have required only routine experimentation and optimization such that one of ordinary skill in the art would reasonably expect that that they could convert Reb D to Reb X with at least about a 50% conversion rate.

In view of the foregoing, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that the subject matter of challenged claims 1–14 would have been obvious over the combined disclosures of Ohta and WO378.

E. Asserted Obviousness of Claims 1–14 over WO227

Petitioner asserts that claims 1–14 would have been obvious over the disclosure of WO227. Pet. 62–67. Patent Owners dispute Petitioner's contentions. Prelim. Resp. 28–31.

1. WO227

WO227 discloses the recombinant production of steviol glycosides, including Reb D and Reb X (referred to in WO227 as Reb M). Ex. 1009 ¶¶ 4, 7. WO227 describes methods of making Reb X by converting Reb D to Reb X using UGT76G1. *Id.* ¶¶ 323–332.

2. Prior Art Status of WO227

Petitioner asserts that WO227 is prior art under 35 U.S.C. § 102(e) because WO227 is entitled to the effective filing date of its provisional application, and the '272 patent is not entitled to the effective filing date of

its provisional application. *See, e.g.*, Pet. 5, 21–26, 35–45. Patent Owners disagree. *See, e.g.*, Prelim. Resp. 10–23.

As noted above, in an *inter partes* review, the burden of persuasion is on the petitioner to prove unpatentability by a preponderance of the evidence, and that burden never shifts to the patent owner. *Dynamic Drinkware*, 800 F.3d at 1378. The petitioner also has the initial burden of production to show that an asserted reference qualifies as prior art under 35 U.S.C. § 102. *Id.* at 1378–79. Once the petitioner has met that initial burden, the burden of production shifts to the patent owner to argue or produce evidence that either the asserted reference does not render the challenged claims unpatentable, or the reference is not prior art. *Id.* at 1379–80 (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)).

A threshold issue, then, is whether Petitioner has met its initial burden to show that WO227 is prior art to the challenged claims. The '273 patent issued on January 26, 2016 from an application filed on August 26, 2014. Ex. 1001, codes (22), (45). The '273 patent is a continuation of Application No. PCT/US2013/030439, which was filed on March 12, 2013. *Id.* at codes (22), (63). The '273 patent also claims priority to provisional application 61/649,978 (Ex. 1002, "the '978 provisional"), which was filed on May 22, 2012. *Id.* at code (60).

WO227 was filed on February 6, 2014 and published on August 14, 2014. Ex. 1009, codes (22), (43); Pet. 5. WO227 also claims priority to provisional application nos. 61/761,490 ("the '490 provisional," filed on February 6, 2013), and 61/886,442 ("the '442 provisional," filed on October 3, 2013). Ex. 1009, code (30); Pet. 5.

Petitioner and Dr. Walters present evidence that the '490 provisional provides a sufficiently enabling written description for the invention claimed in WO227. Pet. 21–26 (citing Ex. 1003 ¶¶ 37–45). For example, claim 1 of WO227 recites a "composition comprising from about 1% to about 99% w/w of Rebaudioside M, wherein the composition has a reduced level of Stevia-derived contaminants relative to a stevia extract." Ex. 1009, 109. 11 According to Petitioner, written description support for this claim is found, for instance, in Examples 2 and 3 of the '490 provisional, which describe a biocatalytic reaction using purified UGT76G1 and Reb D to produce a highly pure Reb M fraction. Pet. 23 (citing Ex. 1010, 61–63¹²). Petitioner also presents evidence that the disclosure in WO227 relied upon by the Petitioner in its obviousness and anticipation arguments, is supported by the '490 provisional. See Pet. 62–71 (providing supporting citations to Ex. 1010). On this record, we are persuaded that Petitioner has satisfied its initial burden that the claims and disclosure of WO227 are entitled to the filing date of the '490 provisional. See Dynamic Drinkware, 800 F.3d. at 1381 ("A reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with $\S 112, \P 1.$ ").

Petitioner also asserts that the claims of the '273 patent are not entitled to the priority date of the '978 provisional. Pet. 35–49. Patent

-

¹¹ The cited page numbers in Ex. 1009 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

¹² The cited page numbers in Ex. 1010 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

IPR2019-01017 Patent 9,243,273 B2

Owners disagree. Prelim. Resp. 10–23. These arguments are discussed below.

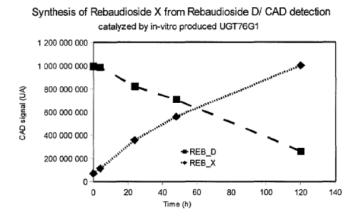
a. Principles of Law Regarding Claims of Priority to a Provisional Application

Claims in a patent are entitled to the benefit of a prior filed provisional application under 35 U.S.C. § 119(e) if the provisional application supports the claims in the way required by 35 U.S.C. § 112 ¶ 1. See Dynamic Drinkware, 800 F.3d at 1378. "In other words, the [S]pecification of the provisional must 'contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms, 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention claimed in the non-provisional application." Id. (citing New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1294 (Fed. Cir. 2002)). Although the written description requirement does not require the applicant "to describe exactly the subject matter claimed," the application "must describe the later claimed invention 'in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." In re Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989); see also Tech. Licensing, 545 F.3d at 1331 (citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)).

b. Analysis of Priority Date of the Challenged Patent
Petitioner asserts that the '978 provisional "would not reasonably
convey to a person of ordinary skill in the art that the inventors were in
possession of a method of converting reb D to reb X, wherein conversion is
at least about 50% complete" and, therefore, the "claims of the '273 patent

are not supported by the '978 provisional." Pet. 45. Specifically, Petitioner contends that the '978 provisional "does not reasonably inform the [person of ordinary skill in the art] of how much reb D was converted to reb X according to the method described in Example 6." *Id.* at 41 (citing Ex. 1003 ¶ 82).

Petitioner argues that Example 6 of the '978 provisional is the only working example of a method of converting Reb D to Reb X using a UGT enzyme. Pet. 37. Example 6 states that there was an 80% conversion of Reb D to Reb X after 120 hours; however, Petitioner contends that the only "purported support" for this conversion is in the following figure from the '978 provisional:



Id. at 37 (citing Ex. 1002, 22¹³). The figure depicts the synthesis of Reb X from Reb D using CAD detection, plotting CAD signal versus time.

Petitioner asserts that the measurement method used for the above figure, HPLC-CAD, is not described in the '978 provisional and is not commonly used in the art to characterize and/or quantify substances.

Pet. 38. Petitioner contends, with supporting testimony from Dr. Walters,

¹³ The cited page numbers in Ex. 1002 are to the pages added by Petitioner in the bottom-right corner of the page.

that "a CAD signal alone does not inform the [person of ordinary skill in the art] of what substance is present" and, "[i]n contrast, other analytical techniques typically used with HPLC, such as NMR and mass spectrometry, provide structural information about the substance." *Id.* at 39 (citing Ex. 1003 ¶¶ 59–60, 80). Petitioner further asserts that, although the '978 provisional includes an infrared adsorption spectrum of Reb X in Figure 4, the '978 provisional does not state that the spectrum was obtained with Reb X produced according to the procedures in Example 6 or used to confirm the identity of the Reb X component in the HPLC-CAD figure. *Id.*

In support of the argument that CAD is not a reliable method of quantification, Petitioner cites to Robinson,¹⁴ which states that "it seems to be widely accepted that CAD is an 'approximate' mass detector with an almost universal response that seems largely independent of the physical or chemical properties of the analyte. Previously, the variable CAD response has been put down to differences in volatility, ion-pairing, and more recently density." Pet. 39–40 (quoting Ex. 1035, 2¹⁵). Petitioner also asserts that "treating CAD as a mass detector often results in quantification errors" and, according to Robinson, "the average quantification error among 50 compounds tested was 11.4%" and "[f]or highly dense compounds, the average quantification error was 34.7%." *Id.* at 40 (citing Ex. 1035, 1; Ex. 1003 ¶ 81). According to Petitioner, "[t]here is no evidence in the '978 Provisional that the inventors recognized the unreliability of quantifying

_

¹⁴ Robinson, Max W., et. al., *Use of Calculated Physicochemical Properties to Enhance Quantitative Response When Using Charged Aerosol Detection*, American Chemical Society, Analytical Chemistry, Vol. 89, 1772–1777 (2016) (Ex. 1035, "Robinson").

¹⁵ The cited page number in Exhibit 1035 refer to the numbers added by Petitioner in the bottom-right corner of the page.

substances using CAD or attempted to address these issues in some way, such as by calibrating the instrument using a known standard." *Id.* at 40–41 (citing Ex. $1003 \, \P \, 82$).

Petitioner further asserts that, "[o]ther than claiming to have used [HPLC-CAD], the inventors do not describe how they separated Reb D and Reb X, how they confirmed Reb D and Reb X were adequately separated to allow for accurate quantification, nor do they even explain how they determined that Reb X and Reb D were present." Pet. 42 (citing Ex. 1003 ¶ 84). Petitioner concludes that the '978 provisional "does not inform the [person of ordinary skill in the art] of how much Reb D was converted to Reb X according to the method described in Example 6." *Id.* at 43 (citing Ex. 1003 ¶ 86).

Petitioner also compares Example 6 of the '978 provisional with Example 14 of the '273 patent to support its argument that Example 6 did not actually result in an 80% conversion of Reb D to Reb X. Pet. 43–45. Example 14 of the '273 patent describes the transformation of Reb D to Reb X and provides the HPLC conditions and procedure used to separate and identify the reaction components. Ex. 1001, 26:50–27:11. Petitioner's Declarant, Dr. Walters, determined that there was a 40% conversion from Reb D to Reb X in Example 14. Ex. 1003 ¶¶ 88–89. Because the reaction time in Example 14 was only 90 hours, Dr. Walters then estimated the conversion of Reb D to Reb X in Example 6 of the '978 provisional after 90 hours of reaction time and calculated a conversion of 64.8%. *Id.* ¶ 90. Based on this comparison, Petitioner argues that Example 6 did not result in the claimed 80% conversion rate. Pet. 44 (citing Ex. 1003 ¶ 90).

Patent Owners respond by providing testimony from Dr. Joe P. Foley, Patent Owner's asserted expert in HPLC, stating that HPLC-CAD is a reliable method and standard technique for quantitative analysis of steviol glycosides. Prelim. Resp. 11–12 (citing Ex. 2001 ¶¶ 16–17, 19–20). Patent Owners also cite to several textbooks and references to support their contention that HPLC-CAD is a well-recognized technique for measuring steviol glycosides. *Id.* at 12–13 (citing Ex. 2005, 35; Ex. 2006, 56–57; Ex. 2007, 4; Ex. 2008, 5).

With regard to the Robinson article cited by Petitioner, Patent Owners cite to the portion in Robinson which states that "CAD also gives a more universal response between analytes, with the most recent versions reported to have an interanalyte response across a broad range of compounds on the order of <11% (relative standard deviation of the response of 24 × 1.0 μg samples)." Prelim. Resp. 15 (citing Ex. 1035, 1). According to Patent Owners and Dr. Foley, Robinson explains that low molecular weight compounds (less than 300 Daltons), high density compounds, and basic compounds, experience systematic errors with CAD, while steviol glycosides have high molecular weight, do not have high density, and are not basic. *Id.* (citing Ex. 1035, 5; Ex. 2001 ¶ 22). Therefore, according to Patent Owners, the concerns expressed by Robinson regarding use of HPLC-CAD with certain molecules do not apply to the '273 patent steviol glycosides. *Id.*

Patent Owners further argue that the error rate referenced in Robinson is too small to matter for the claims at issue. Prelim. Resp. 18–20. Specifically, Robinson states that the average error rate for HPLC-CAD is 11.4%. Ex. 1035, 1. Using this error rate, Patent Owners, with supporting

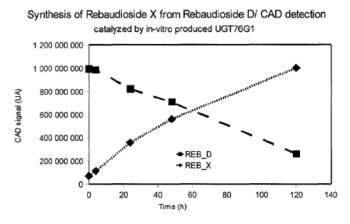
testimony from Dr. Foley, assert that the 80% conversion shown in Example 6 of the '978 provisional would, at worst, be 75%, which would still satisfy the claim 1 limitation of "at least about 50%." Prelim. Resp. 19–20 (citing Ex. 2001 ¶¶ 29–30; Ex. 2002 ¶¶ 63–66).

Patent Owners also contend that Petitioner's comparison of Example 6 from the '978 provisional and Example 14 from the '273 patent is not appropriate. Prelim. Resp. 16–17. With supporting testimony from Drs. Foley and Williams, Patent Owners assert that these experimental examples are too different for any comparisons to be made. *Id.* at 17 (citing Ex. 2001 ¶ 27; Ex. 2002 ¶¶ 69–74 (discussing how the examples use different concentrations of UDP-glucose, different preparations of UTG76G1, are run for different time periods, and target different reaction points)).

Lastly, Patent Owners argue that the invention of the '273 patent is the conversion of Reb D to Reb X, and not the HPLC technique used to measure it. Prelim. Resp. 20. According to Patent Owners, Petitioner does not contest that the '978 provisional describes the enzymes used to convert Reb D to Reb X, how to make these enzymes, and the reaction conditions necessary to convert Reb D to Reb X at a conversion of at least 50%. *Id.* at 20–21 (citing Ex. 2002 ¶¶ 58–61). Patent Owners further argue that "even if the inventors' proof that the conversion recorded in Example 6 converted 80% of Rebaudioside D to Rebaudioside [X] were inadequate, as Petitioner contends, there is no reasonable dispute regarding whether the inventors disclosed that their invention achieved this result" and that disclosure is, therefore, enough to support the written description requirement. *Id.* at 22. Patent Owners also assert that the invention, as disclosed in the '978

provisional, "is routinely used by PureCircle, and by SweeGen, to convert Rebaudioside D to Rebaudioside [X] with at least about 50% conversion" and is, therefore, enabled. *Id.* at 23

On this record, we are persuaded that Patent Owners have satisfied their burden that the claims of the '273 patent are entitled to the filing date of the '978 provisional. Example 6 of the '978 provisional describes the conversion of Reb D to Reb X using UGT76G1. Ex. 1002, 21–22. The '978 provisional also describes how to make the UGT76G1 enzyme used in the example, and provides reaction conditions such as temperature, time, concentrations, reactants, and stirring speed for the conversion reaction. Ex. 1002, 19–22; *see* Ex. 2002 ¶ 60. The results of the conversion reaction described in Example 6 are shown in the figure below from the '978 provisional:



Ex. 1002, 22. The figure illustrates the amount of conversion of Reb D to Reb X at various time points, including 50% conversion, and up to 80% conversion after 120 hours. *Id.* The '978 provisional also states that, in an embodiment of the invention "a biocatalytic system capable of producing UDP-glucose is introduced into the host [] for the hyperproduction of said molecule necessary for high yield conversion of steviol glycosides." Ex. 1002, 10.

With regard to Petitioner's assertions concerning the weaknesses of HPLC-CAD, Patent Owners have persuasively shown with supporting evidence and testimony that HPLC-CAD is a reliable technique used to analyze steviol glycosides. Prelim. Resp. 11–18. Furthermore, any potential error in the HPLC-CAD method, as discussed in Robinson, would not have materially affected the conversion value. *Id.* at 18–20.

Based on the information disclosed in the '978 provisional and the current record, we are persuaded that the '978 provisional describes the invention in "sufficient detail" such that "one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Tech. Licensing*, 545 F.3d at 1331 (citing *Lockwood*, 107 F.3d at 1572). Accordingly, the record before us does not support Petitioner's contention that WO227 qualifies as prior art to the '273 patent under § 102(e). Therefore, Petitioner has not established a reasonable likelihood of prevailing on any challenge based on WO227.

F. Asserted Anticipation of Claims 1–6 and 12–14 by WO227
Petitioner asserts that claims 1–6 and 12–14 are anticipated by
WO227. Pet. 67–71. Patent Owners dispute Petitioner's contentions.
Prelim. Resp. 23–28. Because we determine Petitioner has not shown
persuasively that WO227 qualifies as prior art to the '273 patent under §
102(e), as explained above, Petitioner has not established a reasonable
likelihood of prevailing on any challenge based on WO227.

G. 35 U.S.C. § 325(d)

Patent Owners contend we should exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition because both Ohta and WO378 were considered by the Examiner during prosecution of the '273 patent. Prelim.

IPR2019-01017 Patent 9,243,273 B2

Resp. 52–57. Because we have considered the merits of the Petition and decline to institute an *inter partes* review on that basis, Patent Owners' arguments with respect to 35 U.S.C. § 325(d) are moot.

III. CONCLUSION

For the reasons set forth above, Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to challenged claims 1–14 of the '273 patent. Thus, we do not institute an *inter partes* review with respect to the challenged claims.

IV. ORDER

It is

ORDERED that the Petition is *denied* and no *inter partes* review is instituted.

IPR2019-01017 Patent 9,243,273 B2

FOR PETITIONER:

Alton Hare
Ahmed Abdel-Rahman
PILLSBURY WINTHROP SHAW PITTMAN LLP
alton.hare@pillsburylaw.com
ahmed.abdelrahman@pillsburylaw.com

FOR PATENT OWNERS:

Stuart E. Pollack David C. Xu DLA Piper LLP stuart.pollack@us.dlapiper.com david.xu@us.dlapiper.com