

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELIXIS INC.,
Patent Owner.

IPR2025-00210
Patent 11,298,349 B2

Before JEFFREY N. FREDMAN, JEFFREY W. ABRAHAM, and
DAVID COTTA, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Azurity Pharmaceuticals, Inc. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting *inter partes* review of claims 1–3 (the “challenged claims”) of U.S. Patent No. 11,298,349 B2 (Ex. 1001, “the ’349 patent”). Exelixis, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 8 (“Prelim. Resp.”).

We have jurisdiction under 35 U.S.C. § 6 and authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the Petition “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.”

Having considered the arguments and evidence presented in the Petition and the Preliminary Response, for the reasons described below, we do not institute *inter partes* review.

II. REAL PARTIES-IN-INTEREST

Petitioner identifies itself as the real-party-in-interest and identifies Slayback Pharma LLC as a wholly-owned subsidiary of Azurity Pharmaceuticals, Inc. Pet. 67. Patent Owner identifies the real party-in-interest as itself. Paper 3, 2.

III. RELATED MATTERS

Petitioner and Patent Owner identify the ’349 patent as involved in pending litigation including *Exelixis, Inc. v. MSN Laboratories Private Ltd. et al.*, C.A. No. 1:22-cv-00228 (D. Del.), which has been appealed to the U.S. Court of Appeals for the Federal Circuit, Appeal No. 2025-1236, 2025-1241 (Fed. Cir.), and *Exelixis, Inc. v. Sun Pharmaceutical Industries Ltd. et al.*, C.A. No. 1:24-cv-01208 (D. Del.). Pet. 67; Paper 3, 2.

The parties also identify a number of related patents and patent applications including US 9,717,720; U.S. 10,123,999; US 10,543,206; US 12,128,039; US Application Serial Numbers: 16/706,323; 17/152,394; 17/497,201; 17/957,505; 18/462,739; 17/679,634; and 18/899,774; and US Provisional Application Serial Number 61,441,520. Pet. 68, Paper 3, 2–3.

IV. THE '349 PATENT

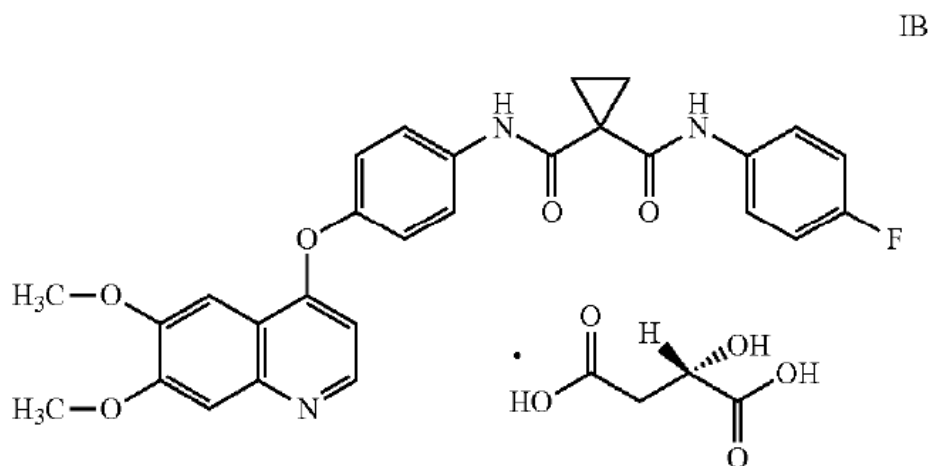
The '349 patent teaches the “disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity.” Ex. 1001, 1:27–29. The '349 patent teaches “signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells.” *Id.* at 1:42–44. The '349 patent explains that “[s]mall-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases . . . are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis.” *Id.* at 2:61–66.

The '349 patent teaches:

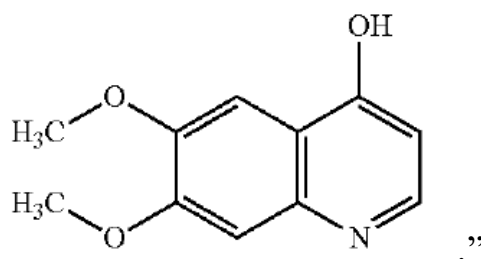
Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

Id. at 3:20–28. The '349 patent states “there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts.” *Id.* at

3:29–32. The formula of compound IB in the '349 patent is reproduced below:



The '349 patent states “the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol . . . the structure of which is



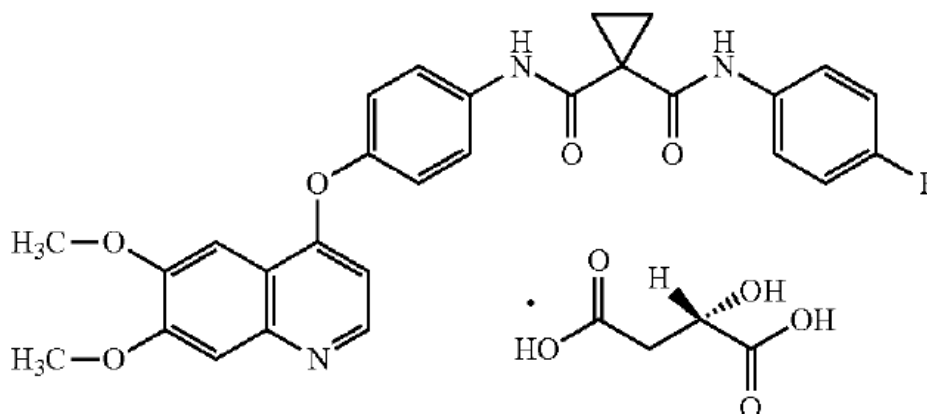
Id. at 22:8–20. The '349 patent states that 6,7-dimethoxy-quinoline-4-ol “can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.” *Id.* at 22:22–27.

V. ILLUSTRATIVE CLAIMS

Petitioner challenges claims 1–3. Claim 1 is representative and reproduced below:

1. A pharmaceutical composition for oral administration comprising Compound IB;

IB



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

Ex. 1001, 34:5–26.

VI. ASSERTED GROUNDS

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 9.

Ground	Reference	Basis	Claims Challenged
1	Wilson ¹	§ 102	1–3

¹ Wilson et al., US 9,717,720 B2, issued Aug. 1, 2017 (“Wilson,” Ex. 1002).

2	Brown, ² Kubo, ³ Remington ⁴	§ 103	1–3
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Petitioner relies, *inter alia*, on the Declarations of Graham Buckton, Ph.D. and William Dichtel, Ph.D. *See* Exs. 1007, 1027.

VII. CLAIM INTERPRETATION

The Board interprets claim terms in an *inter partes* review using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 37 C.F.R. § 42.100(b)). In construing claims, district courts give claims their ordinary and customary meaning, which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

A. Claim 1

Petitioner states

The phrase “essentially free of process byproducts or contaminants” is expressly defined. Ex. 1001 at 8:15-20 (“‘Essentially free’ as used in the phrase ‘essentially free of process byproducts or contaminants,’ means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.”); Ex. 1007 ¶36. This definition has been applied in this petition. Ex. 1007 ¶36.

Pet. 10–11.

² Brown et al., WO 2010/083414 A1, published July 22, 2010 (“Brown,” Ex. 1003).

³ Kubo et al., US 7,169,789 B2, issued Jan. 30, 2007 (“Kubo,” Ex. 1028).

⁴ *Remington: The Science and Practice of Pharmacy*, 21st Edition, pp. 889–928 (2005) (“Remington,” Ex. 1004).

Patent Owner does not dispute this claim interpretation. *See* Prelim. Resp. 11.

B. Claim 3

Petitioner states

the '349 patent does identify “6,7-dimethoxy-quinoline-4-ol” as “a byproduct that may form during the synthesis of Compound IA or IB” and is to be minimized in pharmaceutical compositions. Ex. 1001 at 22:22-27. Further, in prior litigation, the district court applied a numerical limit of 200 ppm or less for the potentially genotoxic impurity, 6,7-dimethoxy-quinoline-4-ol. Ex. 1026 at 45. Solely for purposes of this petition, Azurity does not contest the accuracy of this construction and has applied it in this petition. Ex. 1007 ¶37.

Pet. 11.

Patent Owner “agrees with the construction of ‘essentially free’ adopted by the district court and referenced by Petitioner.” Prelim. Resp. 11.

Because both parties agree on the claim construction, we construe the claims as proposed by the parties at this stage in the proceeding.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

Petitioner asserts:

a person of ordinary skill in the art (“POSA”) would have had at least a bachelor’s degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. Ex. 1010 ¶11.

Pet. 10 (citing Ex. 1007 ¶ 31, Ex. 1027 ¶¶ 24, 27).

Patent Owner “agrees with Petitioner’s POSA definition, Pet. 10, which is the same definition Patent Owner proposed in district court.” Prelim. Resp. 11.

We agree with the parties at this stage in the proceeding. We also note the level of ordinary skill in the art usually is evidenced by the prior art references themselves. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

IX. ANTICIPATION GROUND

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.” *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

“A specification that ‘reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date’ has adequate written description of the claimed invention.” *Novartis Pharm. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1368 (Fed. Cir. 2022) (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)). “[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.” *Id.* at 1368–69.

“Determining whether claims are anticipated involves a two-step analysis. The first step involves construction of the claims of the patent at issue. Claim construction is a question of law reviewed *de novo*.” *In re*

Aoyama, 656 F.3d 1293, 1296 (Fed. Cir. 2011). “The second step [of an anticipation analysis] involves comparing the claims to the prior art. Anticipation is a question of fact reviewed for substantial evidence.” *Se Id.* at 1296. “A prior art reference anticipates a patent claim under 35 U.S.C. § 102(b) if it discloses every claim limitation.” *In re Montgomery*, 677 F.3d 1375, 1379 (Fed. Cir. 2012). A reference may anticipate inherently if a claim limitation that is not expressly disclosed “is necessarily present, or inherent, in the single anticipating reference.” *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010).

B. Overview of Prior Art cited for Anticipation

1. *Wilson*

Wilson is a U.S. Patent that issued from US application 13/984,559, a grandparent application of the '349 patent and to which the '349 patent claims benefit of priority. Wilson shares the identical Specification as the '349 patent and therefore also teaches the pharmaceutical composition comprising a compound of Formula IB “admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol.” Ex. 1002, 7:28–29. Table 3 of Wilson discloses an exemplary capsule composition and is reproduced below:

TABLE 3

Ingredient	mg/unit dose
Compound IB (10% drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

Table 3 discloses a capsule that comprises microcrystalline cellulose, a type of filler, croscarmellose sodium and sodium starch glycolate as types of disintegrants, fumed silica as a type of glidant, and stearic acid as a type of lubricant. Ex. 1002, 20:51–62, 32:24–40.

C. Priority

The priority dispute centers around whether Wilson qualifies as prior art. Petitioner acknowledges that Wilson is a member of the same patent family as the '349 patent and is a priority document for the '349 patent, but asserts that Wilson fails to provide written description support for the claims of the '349 patent. *See, e.g.*, Pet. 11–12. Patent Owner disagrees, noting no procedural break in priority so Wilson does not qualify as prior art. *See, e.g.*, Prelim. Resp. 12–13.

1. Petitioner's position

Petitioner asserts “to satisfy the written description requirement, the priority applications must convey possession of the full scope of the Challenged Claims – including the innumerable permutations of excipients within a composition that achieves impurity levels below 200 ppm.” Pet. 13–14. Petitioner asserts that Patent Owner “admitted—in a litigation involving the '349 patent—that the purity of the composition can be impacted by the interaction of Compound IB with excipients in the composition; that those interactions are unpredictable; and that none of this knowledge was in the prior art.” *Id.* at 14 (citing Ex. 1019 at 712:19–713:2). Petitioner asserts: “[g]iven the unknown interactions, and impurity-producing impacts, of these countless excipients, Patentee’s attempt to claim the universe is not justified. Neither the specification in the '349 Patent, nor any of its progenitor

applications, provide sufficient information to justify a claim so broad.” *Id.* at 15 (citing Ex. 1007 ¶¶ 87–122).

Petitioner points to the identical disclosure of the filler, disintegrant, glidant, and lubricant disclosure in Wilson as found in the ’349 patent and asserts this disclosure “does not provide written description for any excipient in these categories—particularly where the overall composition must possess a specified purity level.” *Id.* at 21. Petitioner similarly points to the results in Tables 7A and 8A of Wilson, based on the specific compositions in Tables 3 and 4 in Wilson, identical to the same tables in the ’349 patent, and asserts “[n]o information can be extrapolated from this data regarding the selection of any other excipient—as Exelixis and its experts have admitted.” Pet. 24 (citing Ex. 1019 at 712:15–713:14, 730:16–20, 733:9–14, 733:21–734:13).

2. Patent Owner’s position

Patent Owner asserts “Petitioner fundamentally misconstrues the standard for written description. Written description does not require the disclosure of every possible combination in a pharmaceutical composition.”

Prelim. Resp. 15. Patent Owner asserts

the ’559 application includes: (1) an *ipsis verbis* disclosure of the excipient claim terms Petitioner argues are not supported, (2) multiple representative examples of pharmaceutical formulations of cabozantinib (L)-malate that include each claimed excipient type and are described as meeting the claimed purity level, (3) data demonstrating that two of the formulations had the claimed purity, and (4) citation to Remington (which is also incorporated by reference in its entirety) to explain that “[v]arious carriers . . . and known techniques” could be used to make the disclosed pharmaceutical compositions. Together, these disclosures provide written description for the challenged claims.

Id. at 16–17 (alteration by Patent Owner).

Patent Owner asserts “based on the disclosure of the ’559 application that this improved synthesis provided such pure cabozantinib (L)-malate that routine variations within the claimed classes of excipients beyond the specific exemplified formulations could similarly provide pharmaceutical compositions that maintained the claimed purity level, despite potential degradation caused by excipients.” *Id.* at 22.

Patent Owner notes that “Petitioner’s own reliance on Remington in Ground II contradicts its position that Remington is no more than a ‘laundry list.’” *Id.* at 26.

Patent Owner also asserts

Petitioner and its declarant take isolated statements from Exelixis’ district court experts out of context. *See* Pet. 14-15 n.2; Ex. 1007, ¶87. Indeed, several witnesses testified that formulating pharmaceutical compositions with excipients from the claimed categories was well-known in the art. Ex. 2003, 748:7-17; Ex. 2002, 394:21-395:2. With respect to the claimed purity, what Exelixis’ witnesses actually testified was that formulations using API prepared via *prior art* synthesis had variable purity; however, once Exelixis developed the process disclosed in the ’349 patent and its priority applications, it consistently obtained formulations having the claimed purity level using a range of excipients.

Id. at 29–30.

3. *Analysis*

We recognize that one purpose of the written description requirement “is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.” *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). However, written description “is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to

what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue.” *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). That is, the “‘written description’ requirement must be applied in the context of the particular invention and the state of the knowledge.” *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005).

Here, there is no dispute that the ’349 patent and Wilson, which issued from a patent application from which priority was claimed for the ’349 patent, share the identical disclosure of

a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants. In this embodiment, the filler comprises microcrystalline cellulose. In this embodiment, the disintegrant comprises croscarmellose sodium. In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate. In this embodiment, the glidant comprises fumed silica. In this embodiment, the lubricant comprises stearic acid.

Ex. 1001, 21:1–12; Ex. 1002, 20:51–62. There is express *ipsis verbis* disclosure of the elements recited in claim 1 of the ’349 patent.

Moreover, on this record, the prior art is replete with teachings of known fillers, disintegrants, glidants, and lubricants. *See* Ex. 1004, 891; Ex. 1003 ¶¶ 82–87. For example, Remington recites a number of fillers (termed diluents) and demonstrates that the ordinary artisan was aware of parameters guiding selection of diluents for particular active chemical entities. Ex. 1004, 891. Remington also evidences that large numbers of disintegrants, glidants, and lubricants were well known to the person of ordinary skill. *See Id.* at 892–893.

These facts are analogous to the situation in *Alcon*, where the Court found a broad claim to the addition of a stabilizer to an ophthalmic composition compliant with the written description requirement because the patent at issue provided “exemplary formulations that embody the claimed invention” and “describe[d] the various formulation parameters.” *Alcon*, 745 F.3d at 1191. The ’349 patent provides exemplary formulations in Tables 3 and 4, and identifies stability as an important parameter for analysis in Tables 7 and 8. *See* Ex. 1001, 30:65–33:39.

We are unpersuaded by Petitioner’s arguments regarding the unpredictability of the impact of excipients such as fillers, disintegrants, glidants, and lubricants on the active chemical entities as that is drawn to scope of enablement⁵ rather than written description support for priority. Rather, the evidence shows that the excipients recited in the claims of the ’349 patent were all well-known and reasonably comply with the written description requirement. We note that

it is almost always possible to so construe a claim as to have it read on inoperative embodiments. . . . but the alternative of requiring an applicant to be so specific in his claims “as to exclude materials known to be inoperative and [which] even those not skilled in the art would not try” would result in claims which would fail to comply with 35 U.S.C. § 112, second paragraph, because they would be so detailed as to obscure,

⁵ On the current record, Petitioner has not provided evidence addressing the factors in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) and we note that scope of enablement under 35 U.S.C. § 112 is not a proper ground for *inter partes* review. *See* U.S.C. § 311(b) (“A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.”).

rather than to particularly point out and distinctly claim, the invention.

In re Smythe, 480 F.2d 1376, 1385 (CCPA 1973).

Because we find that the '349 patent is entitled to priority at least to Wilson's priority date, Wilson is not prior art to the '349 patent and cannot therefore be relied upon for an anticipation ground.

Accordingly, we find that on the current record Petitioner has not shown that it has a reasonable likelihood that it would prevail on the anticipation ground.

X. OBVIOUSNESS GROUND

A. *Principles of Law*

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). In *KSR*, the Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the answer depends on

“whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417.

The motivation-to-combine analysis is a flexible one. “[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed,” [but the] “analysis ‘need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.’”

Intel Corp. v. PACT XXP Schweiz AG, 61 F.4th 1373, 1379–80 (Fed. Cir. 2023) (quoting *KSR*, 550 U.S. at 418, 420 (emphasis added)). “[I]f there’s a known technique to address a known problem using ‘prior art elements according to their established functions,’ then there is a motivation to combine,” because *KSR* explains that “if a technique has been used to improve one device [or method], and a person of ordinary skill in the art would recognize that it would improve similar devices [or methods] in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *Id.* at 1380 (quoting *KSR*, 550 U.S. at 417; and *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 797 (Fed. Cir. 2021)). If addressing a known problem, the prior art combination need not be “the *best* option, only . . . a *suitable* option.” *Id.* (quoting *Intel*, 21 F.4th at 800 (emphasis in original)).

B. Overview of Prior Art cited for Obviousness

1. *Brown (Ex. 1003)*

Brown is an international patent publication titled to “Malate Salt of [Cabozantinib], and Crystalline Forms Thereof for the Treatment of Cancer.” Ex. 1003, code [54]. Brown states the salt form of the compound

“has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms.” *Id.* ¶ 12.

Brown identifies preparative examples for the compound showing the chemical synthetic route. *Id.* ¶¶ 98–134. Brown states the

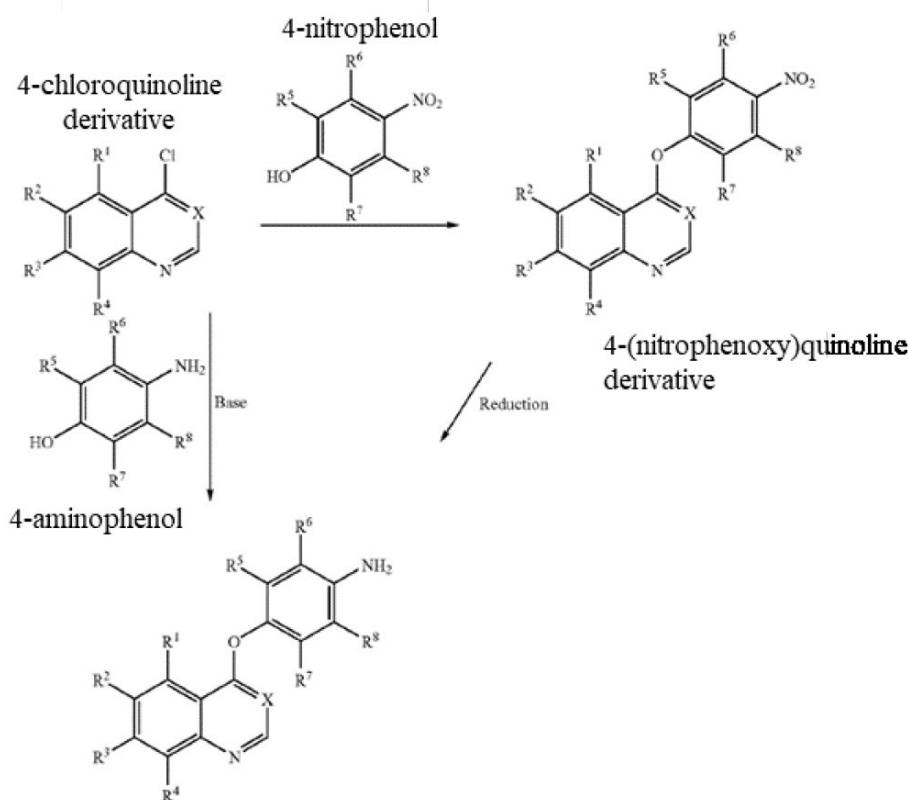
pharmaceutical compositions of this disclosure may be prepared by methods know[n] in the pharmaceutical formulation art, for example, see Remington’s Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof.

Id. ¶ 82.

2. *Kubo (Ex. 1028)*

Kubo is a U.S. Patent titled “Quinoline Derivatives And Quinazoline Derivatives.” Ex. 1028, code [54]. Kubo states an “object of the present invention is to provide compounds which have antitumor activity and, at the same time, have no significant effect on cytomorphosis.” *Id.* at 1:29–31.

Kubo states the “compounds according to the present invention may be produced, for example, according to scheme 1 and scheme 2.” *Id.* at 10:42–44. Kubo states that synthesis begins with a 4-chloroquinoline derivative through one of the two schemes depicted below.



Pet. 34 (annotations added by Petitioner) (citing Ex. 1028, 11:1–12:40.)

3. *Remington (Ex. 1004)*

Remington is a textbook titled “Remington: The Science and Practice of Pharmacy.” Ex. 1004, 1. Chapter 45 of Remington states “[d]rug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules.” *Id.* at 889. Remington states:

Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to facilitate handling,

enhance the physical appearance, improve stability, and aid in the delivery of the drug to the bloodstream after administration.

Id. Remington identifies additives including “diluent, binders, glidants, and lubricants” as well as “disintegrants, surfactants, colors, and, in the case of chewable tablets, flavors, and sweetening agents, and in the case of controlled-release tablets, polymers or hydrophobic materials, such as waxes or other solubility-retarding materials.” *Id.* at 891.

C. Petitioner’s position

Petitioner challenges claims 1–3 of the ’349 patent as obvious over Brown, Kubo, and Remington. Pet. 36–61.

1. *Claim 1*

Petitioner contends “Brown teaches the inclusion of cabozantinib (L)-malate (i.e., ‘Compound IB’) in a pharmaceutical composition.” Pet. 36 (citing Ex. 1003 ¶¶ 2, 51, 52, 54, 66, 77, 78; Ex. 1007 ¶ 174). Petitioner contends

Brown teaches the inclusion of “fillers.” Ex. 1003 at [0082]; Ex. 1007 ¶178. Remington also teaches that fillers (i.e., “diluent”) are added to tablet formulations to facilitate manufacturing. Ex. 1004 at 891; Ex. 1007 ¶179. Moreover, Remington says it is “obvious” to include a filler “to make tableting possible.” Ex. 1004 at 891.

Id. at 37. Petitioner similarly contends that Brown and Remington suggest the use of disintegrants, glidants, and lubricants in a capsule formulation. *Id.* at 37–44.

Petitioner contends “it would have been obvious to obtain a tablet or capsule composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol.” Pet. 44. Petitioner contends “Brown indicates that 6,7-dimethoxy-quinoline-4-ol can remain as a ‘reaction impurity,’ whose

presence in cabozantinib (L)-malate ‘may be determined by analytical techniques known in the art.’” *Id.* at 45–46 (citing Ex. 1003 ¶¶ 97, 102; Ex. 1027 ¶ 54). Petitioner contends “Brown’s cabozantinib (L)-malate contained ‘at most, de minimis’ 6,7-dimethoxy-quinoline-4-ol.” *Id.* at 46 (citing Ex. 1026, 46).⁶

Petitioner contends that “Kubo teaches that the two steps of Brown . . . can ‘[a]lternatively’ be performed in a single step using 4-aminophenol.” *Id.* at 48 (citing Ex. 1028 at 12:46–14:4; Ex. 1027 ¶¶ 60–64). Petitioner contends “a POSA would have been motivated to apply Kubo’s one-step alternative to Brown’s preparation of cabozantinib (L)-malate. Ex. 1027 ¶¶ 65–74. The single-step approach saves one step in Brown’s synthesis of cabozantinib (L)-malate.” *Id.* at 49 (citing Ex. 1027 ¶¶ 57–60, 66). Petitioner contends that

Kubo’s alternative use of 4-aminophenol saves money by eliminating unnecessary chemical usage and waste disposal from the unnecessary reaction. Ex. 1027 ¶ 69. It saves manpower by eliminating performance of the unnecessary reaction. Ex. 1027 ¶ 69. It eliminates a hazardous reagent. Ex. 1035 at 124440; Ex. 1027 ¶ 69. It saves in material costs because . . . it was known that

⁶ The full quote of the Delaware District Court findings 9 and 10 regarding obviousness states

9. MSN has not shown by clear and convincing evidence that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (FOF ¶ 8).

10. A POSA would not be motivated to minimize the 1-1 impurity after the Brown process because a POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process. Each step of the Brown process purifies the API. (Tr. 668:16–669:14, 708:23–709:19).

Ex. 1026, 46.

the one-step approach can afford the same compound in as much as a 92% yield. . . . Kubo also teaches that the one-step approach can simplify product isolation and improve purity. Ex. 1028 at 12:60–14:2; Ex. 1027 ¶¶73–74.

Id. at 51. Petitioner contends “[b]y applying Kubo’s one-step approach with 4-aminophenol to Brown’s synthesis of cabozantinib (L)-malate, a POSA would have expected lower amounts of 6,7-dimethoxy-quinoline-4-ol to be present as a result of the difference in hydrolytic stability.” *Id.* at 53 (citing Ex. 1027 ¶ 78).

Petitioner contends that “the one-step approach is the only difference between Brown’s approach to cabozantinib (L)-malate and the ’349 patent’s approach” and “[t]hus, applying the one-step approach of Kubo must necessarily result in cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol.” *Id.* at 54 (citing Ex. 1027 ¶ 80).

As an alternative to inherency, Petitioner contends “a POSA would have been motivated to prepare a composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol due to the chemical structure of this impurity.” *Id.* at 57 (citing Ex. 1007 ¶¶ 204–206). Petitioner contends “a POSA would have known that a quinoline-containing compound such as 6,7-dimethoxy-quinoline-4-ol is potentially genotoxic” and “[a]s such, a POSA would have heeded regulatory guidance regarding the identification and treatment of potentially genotoxic impurities such as 6,7-dimethoxy-quinoline-4-ol.” *Id.* (citing Ex. 1019 at 769:5–770:4; Ex. 1007 ¶¶ 204–206). Petitioner contends “[r]egulatory guidance teaches that the level of a genotoxic impurity should range from less than 120 µg/day to less than 1.5 µg/day depending upon duration of treatment.” *Id.* at 58 (citing Ex. 1037 at 7, 11 (Table 1); Ex. 1038 at 6–7; Ex. 1007 ¶ 206). Petitioner concludes

“[a]ccordingly, it would have been *prima facie* obvious to minimize the amount of 6,7-dimethoxy-quinoline-4-ol to less than 200 ppm per regulatory guidance.” *Id.*

2. Claims 2 and 3

Petitioner contends, for both claims, that the reasons already given make these claims obvious. Pet. 60.

D. Patent Owner’s position

Patent Owner contends

Petitioner relies on Brown, the same key prior art considered by the district court, but fails to acknowledge the court’s findings in support of its determination that challenged claim 3 was not obvious—including that a POSA would not have been motivated to control for 6,7-dimethoxy-quinoline-4-ol in Brown’s synthesis of cabozantinib (L)-malate and that a POSA would not have been motivated to obtain a cabozantinib (L)-malate formulation essentially free of 6,7-dimethoxy-quinoline-4-ol.

Prelim. Resp. 33 (citing Ex. 1026, 46, 51–53, 67; footnote omitted).

Patent Owner contends “Petitioner does not argue that Brown, Kubo, and Remington, alone or in combination, teach or suggest cabozantinib (L)-malate API containing 200 ppm or less of process byproducts or contaminants.” *Id.* at 34. Patent Owner contends “Brown does not identify *any* specific ‘reaction impurities and/or processing impurities’ that might be of concern when synthesizing cabozantinib (L)-malate.” *Id.* at 35 (citing Ex. 1003 ¶ 97; Ex. 2003, 708:14–20).

Patent Owner contends that

Petitioner distorts the district court testimony of Exelixis’ experts to argue that “Brown’s cabozantinib (L)-malate contained ‘at most, de minimis’ 6,7-dimethoxy-quinoline-4-ol.” Pet. 46. However, the district court testimony was not that Brown’s cabozantinib (L)-malate *contained* de minimis 6,7-dimethoxy-

quinoline-4-ol, but rather that a POSA would not have *expected* 6,7-dimethoxy-quinoline-4-ol to be present at the end of the synthetic process and, as a result, would not have thought to control for it in the synthetic process or in the final pharmaceutical formulation.

Id. at 36 (citing Ex. 2002, 669:3–5; Ex. 1026, 49). Patent Owner contends “the testimony was that a POSA would have *expected* ‘de minimis’ 6,7-dimethoxy-quinoline-4-ol from the Brown synthesis, but surprisingly, the synthesis *in fact produced* greater amounts.” *Id.* at 38. Patent Owner also contends “Kubo never identifies 6,7-dimethoxy-quinoline-4-ol (or, indeed, any quinoline) as the decomposition product.” *Id.*

Patent Owner contends “without any motivation to improve purity *in the Brown process* (which the Petition neither argues nor provides evidence to support), this generic possibility of potentially ‘improv[ing] purity’ with Kubo would not provide a motivation to modify Brown to achieve the claimed purity limitation.” *Id.* at 47.

Patent Owner contends

Exelixis made numerous, significant changes to the Brown process—over an eight-year period—to address formation of the 1-1 impurity during synthesis of the 1-3 intermediate, malate salt formation, and drug formulation. Ex. 2002, 671:10-20. Specifically, those changes included: (1) eliminating the 1-3 intermediate that degrades to 1-1; (2) replacing the 4-nitrophenol reagent in step two with 4-aminophenol; (3) replacing the mild 2,6-lutidine base in step two with a much stronger alkoxide base; and (4) modifying the final malate salt formation step to (a) use vacuum distillation (reducing the heat and water required in the reaction) and (b) replace the acetone solvent with methyl ethyl ketone, which has very different chemical properties.

Id. at 39 (citing Ex. 1013 ¶ 54; Ex. 1018, 43; Ex. 2002, 693:14–17, 694:13–695:6). Patent Owner contends “Petitioner never actually argues that any

specific proposed pathway for synthesis of cabozantinib (L)-malate followed by formulation into a composition containing the claimed excipients necessarily or naturally would have resulted in a composition having the requisite purity, as required for inherency.” *Id.* at 41.

E. Analysis

On the current record, the evidence better supports Patent Owner’s position.

1. Reason to reduce contaminant levels

We agree with Patent Owner that Petitioner identifies no teaching in the prior art providing any reason to reduce levels of 6,7-dimethoxyquinoline-4-ol specifically. And while Brown does teach a desire to form “substantially pure” compounds, Brown focuses on “at least about 90 wt.%” of the compound, then lists specifically “about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %.” Ex. 1003 ¶ 97. This permits a range of concentration for contaminants from about 0 to 10%.

Claim 1 of the ’349 patent requires the composition be “essentially free” of contaminants, and the ’349 patent defines “essentially free” as “200 parts per million (ppm) or less of such byproducts or contaminants.” Ex. 1001, 8:15–20, 34:25. We note that 200 ppm is 0.02%, a value within the range recited by Brown. *See, e.g.*, Ex. 2002, 688:6. We also recognize that Dr. Buckton states “a POSA would have been motivated to prepare a pharmaceutical composition that limited impurities, to the extent possible and certainly to within acceptable limits.” Ex. 1007 ¶ 204.

Dr. Lepore acknowledges that Brown provides no guidance on impurities of cabozantinib (L)-malate that would be administered to patients.

See Ex. 2001, 328–329. Dr. Lepore also acknowledges that “Brown does not explicitly state that the 1-1 compound is genotoxic.” Ex. 2001, 330:6–7. Even if we understood Brown as suggesting reducing contaminants, there is no indication in Brown, Kubo, or Remington that amounts as low as 200 ppm of impurities would be necessary for use in patient populations. And Petitioner provides no persuasive evidence or explanation of the Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches that suggests otherwise. *See* Ex. 1037.

We also agree with Patent Owner that there would have been no motivation to purify the composition in order to remove 6,7-dimethoxyquinoline-4-ol. Dr. Lepore, on cross-examination, agreed with the statement that “impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations than impurities generated late in the manufacturing process.” Ex. 2002, 357:11–14.

Dr. MacMillan, a Princeton professor and Nobel prize winner in Chemistry testified in *Exelixis, Inc. v. MSN Lab'ys Priv. Ltd.*, No. CV 22-228-RGA, 2024 WL 4491176 (D. Del. Oct. 15, 2024). *See* Ex. 2001. Dr. MacMillan, in direct testimony, explained why knowing contamination is present is critical to the motivation to purify, stating: “if they don’t believe that it would be there, they would have no expectation it would be there. There would not be a motivation to control for it.” Ex. 2002, 669:12–14. On cross examination, Dr. MacMillan stated regarding the contaminant that “[i]f the POSA believes that it’s not there, there’s no reason to monitor to for it.” *Id.* at 680:14–15. Dr. Myerson, a professor of chemical engineering at MIT and testifying in the same proceeding as Dr. MacMillan, stated that, unlike

prior processes, low 6,7-dimethoxy-quinoline-4-ol levels was “the key feature of the ’349 patent because it teaches a POSA how to make cabozantinib(L)-malate with exceptionally low levels of the 1-1 impurity [6,7-dimethoxy-quinoline-4-ol].” *Id.* at 698:4–7. Dr. Myerson agreed that, reviewing Brown, the presence of 6,7-dimethoxy-quinoline-4-ol “would not be expected by a person of ordinary skill.” Ex. 2003, 709:19.

Dr. Myerson stated that even if a purification step of recrystallization was performed, it would not necessarily have been expected to remove the impurity:

[W]e’re trying to reduce an impurity to below 200 PPM which is 0.02 percent. And the 1-1 impurity [6,7-dimethoxy-quinoline-4-ol] is structurally similar to the API cabozantinib (L)-malate. And often in crystallizations, when have you structurally similar materials, the impurity substitutes in the crystalline lattice as an impurity making it very difficult to achieve that level of purification. This is something I’ve been doing for more than 40 years. Crystallization is one of my main areas, and I’ve seen this in many cases when you’re trying to reduce impurities to very low levels. They just won’t be removed. So you have to come up with a different separation process or different synthetic process to achieve that level of purity.

Id. at 735:10–23.

Accordingly, the evidence of record does not provide a reason to ensure the absence of any particular impurity from cabozantinib (L)-malate, and in particular, no reason to ensure the absence of 6,7-dimethoxy-quinoline-4-ol.

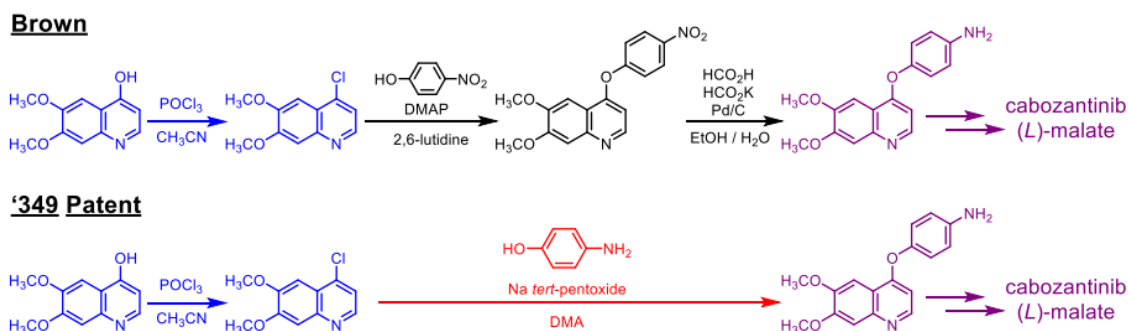
2. Inherent absence of contaminants in Brown

Brown is silent regarding the presence of any specific impurities in a cabozantinib (L)-malate composition. While addressing anticipation, not obviousness, the Court has explained that “when the reference is silent about

the asserted inherent characteristic, . . . evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.” *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Petitioner has provided no persuasive evidence showing that Brown’s method of synthesis and composition would necessarily result in less than 200 ppm of any impurity, much less 6,7-dimethoxy-quinoline-4-ol.

Dr. Buckton, Petitioner’s expert, does not opine on whether the amount of contaminants in the Brown mixture would inherently comply with the recitation of claims 1–3 of the ’349 patent. *See, e.g.*, Ex. 1007 ¶¶ 202–229. Dr. Dichtel presents a figure showing a comparison of the synthetic routes in Brown and in the ’349 patent., which is reproduced below:



“Figure 1. Comparison of synthetic routes in Brown and the [’]349 Patent.” Ex. 1027 ¶ 49. It is immediately evident that these synthetic routes differ by eliminating a synthesis step. And Dr. Dichtel states “if present, 6,7-dimethoxy-quinoline-4-ol *may* be carried through Brown’s synthesis as an impurity.” *Id.* ¶ 54 (emphasis added). Dr. Dichtel does not state that the impurity is necessarily and inherently present, but only that it is possibly present.

Similarly, other evidence of record shows that 6,7-dimethoxy-quinoline-4-ol is a starting component for the synthesis of cabozantinib (L)-malate that may contaminate final compositions and that it may increase in amount in final compositions as a result of degradation of cabozantinib (L)-malate during later processing steps. *See* Ex. 2003, 711:19–22, 712:22–713:5. Dr. Dichtel states “that 6,7-dimethoxy-quinoline-4-ol *may exist* as a reaction impurity in Brown’s cabozantinib (L)-malate and *may be* readily detected.” Ex. 1027 ¶ 54 (emphasis added). Dr. Dichtel states “a POSA would not necessarily expect the 6,7-dimethoxy-quinoline-4-ol to be present in detectable amounts in the cabozantinib (L)-malate obtained by Brown’s process.” *Id.* ¶ 55.

We recognize that Dr. Dichtel asserts that it would have been obvious to modify Brown’s process with Kubo to eliminate the added step. *See, e.g., Id.* ¶ 73. But even with that combination, Dr. Dichtel states only that a “POSA would have expected there to be a decrease in the amount of 6,7-dimethoxy-quinoline-4-ol at the end of cabozantinib (L)-malate’s synthesis that was attributable to hydrolytic degradation of the 4-(nitrophenoxy)quinoline intermediate by avoiding its use in the synthesis.” *Id.* ¶ 78. That is not, however, the standard for inherency. It must be the necessary result, not a possible expected result. The Federal Circuit in *Par* explained that:

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

PAR Pharm., Inc. v. TWI Pharm. Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2014) (citing *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)).

Accordingly, we find that on the current record Petitioner has not shown that the combination of Brown, Kubo, and Remington would inherently result in less than 200 ppm impurity and Petitioner has not shown that it has a reasonable likelihood that it would prevail on the obviousness ground.

XI. DISCRETIONARY DENIAL – 35 U.S.C. §§ 325(d) and 314(a)

In view of our determination that the Petitioner does not meet the threshold for instituting review on the merits, we need not address the parties' dispute about whether the Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d) or under 35 U.S.C. § 314(a). Pet. 61–66; Prelim. Resp. 43–67.

XII. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, we determine that based on the evidence of record that Petitioner has not established that it is more likely than not that claims 1–3 of the '349 patent are unpatentable.

XIII. ORDER

Accordingly, it is

ORDERED that, pursuant to 35 U.S.C. § 314(a), institution of an *inter partes* review of all challenged claims on all grounds presented in the Petition is denied.

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PETITIONER:

Andrew Morrell
Ajay Kayal
Leah Digby
WINDELS MARX LANE
& MITTENDORF, LLP
amorrell@windelsmarx.com
akayal@windelsmarx.com
lkuhn@windelsmarx.com

PATENT OWNER:

Emily Whelan
Cindy Kan
WILMER CUTLER PICKERING
HALE AND DORR LLP
emily.whelan@wilmerhale.com
cindy.kan@wilmerhale.com