

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELIXIS, INC.,
Patent Owner.

Case IPR2025-00427
U.S. Patent No. 12,128,039

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

Institution should be denied because the Petition fails to establish a reasonable likelihood of unpatentability. U.S. Patent No. 12,128,039 (the “’039 patent”) claims a cabozantinib (L)-malate composition containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol, and methods of treating cancer using such a composition. This novel composition resulted from Exelixis’ discovery that an impurity—6,7-dimethoxy-quinoline-4-ol—arose during manufacture of cabozantinib (L)-malate. As of the ’039 patent’s priority date, it was not publicly known that 6,7-dimethoxy-quinoline-4-ol would form as a degradation product (let alone at high levels) or that it was genotoxic. Thus, the need to control 6,7-dimethoxy-quinoline-4-ol was not obvious. Significant, non-routine efforts went into Exelixis’ identification, quantification, and process control of 6,7-dimethoxy-quinoline-4-ol—ultimately resulting in the claimed composition.

Petitioner brings two grounds based on an earlier process for making cabozantinib (L)-malate disclosed in the prior art Brown reference. Brown’s process differs from the improved synthesis disclosed in the ’039 patent, which affords very low levels of 6,7-dimethoxy-quinoline-4-ol. Critically, Brown does not disclose or suggest 6,7-dimethoxy-quinoline-4-ol as genotoxic or a potential degradation product of its process, so it offers no motivation to control for the

presence of 6,7-dimethoxy-quinoline-4-ol during synthesis or formulation of cabozantinib (L)-malate. Neither Kubo (Ground I) nor Robinson (Ground II) can fill this gap to render obvious the claimed 6,7-dimethoxy-quinoline-4-ol levels.

For Ground I, Petitioner asserts that modifying Brown's process for making cabozantinib (L)-malate with a reaction sequence from Kubo would have rendered the purity limitations inherent, but Petitioner does not meet the high bar for showing inherency. Petitioner presents no evidence that the claimed impurity levels (e.g., 100 ppm or less) would have necessarily resulted from its Brown-Kubo synthesis. Petitioner relies heavily on testimony from Exelixis' experts in related district court litigation, *Exelixis, Inc. v. MSN Labs. Private Ltd.*, No. 22-228-RGA (D. Del.) (hereinafter "MSN litigation"), but Petitioner misleadingly presents this testimony out of context. In addition, the patent at issue in that litigation had a less stringent purity limitation (200 ppm or less). Petitioner does not explain how the testimony about expected purity in the MSN litigation would relate to the levels of 6,7-dimethoxy-quinoline-4-ol claimed in the '039 patent (as low as 5 ppm or less). Moreover, Petitioner argues that motivation for combining Brown with Kubo is supposedly to improve efficiency rather than any need to reduce levels of 6,7-dimethoxy-quinoline-4-ol or any other impurity in the Brown process. A general motivation to increase efficiency is insufficient and fails to

(1) acknowledge all the factors a person of ordinary skill in the art (“POSA”) would have considered or (2) account for all the changes that were necessary to arrive at the synthesis disclosed in the ’039 patent.

For Ground II, Petitioner asserts that generic regulatory guidance applicable to *all* pharmaceutical compositions would have prompted a POSA to (1) search for potentially genotoxic impurities in the Brown process, eventually identifying 6,7-dimethoxy-quinoline-4-ol; (2) confirm the genotoxicity of 6,7-dimethoxy-quinoline-4-ol; and then (3) develop strategies to control for it at the claimed levels, specifically by using preparative chromatography. That broad and attenuated series of steps is insufficient to show obviousness. Petitioner also fails to demonstrate why a POSA would have been motivated (a) to control the presence of 6,7-dimethoxy-quinoline-4-ol in cabozantinib (L)-malate by making a process change (i.e., adding a purification step), rather than any of the other “industry approach[es]” identified by Robinson; or (b) to use preparative chromatography as the purification method based on Robinson’s disclosure of a specific chromatography method developed for separating a *different* impurity from a *different* active pharmaceutical ingredient (“API”). Petitioner also fails to show a reasonable expectation of success, i.e., that preparative chromatography, including

the specific method identified by Petitioner, would work in combination with Brown to achieve the challenged purity limitations.

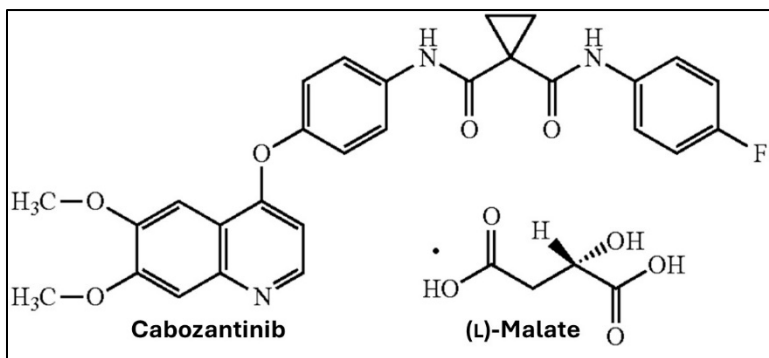
Ultimately, both of Petitioner's grounds ignore that it took Exelixis eight years and multiple significant changes to the Brown process to achieve the purity limitations in the challenged claims. Petitioner's hindsight-driven theories should be rejected.

For at least the foregoing reasons, institution should be denied.

II. BACKGROUND

A. Cabozantinib (L)-Malate

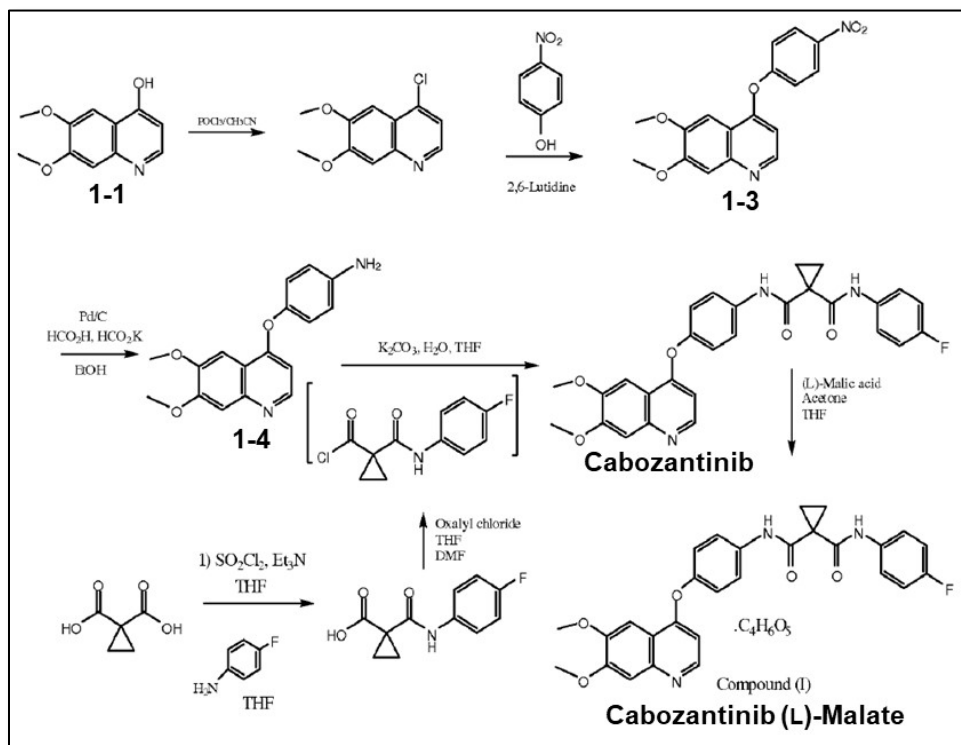
Cabozantinib (L)-malate is the API in Exelixis' approved CABOMETYX[®] and COMETRIQ[®] cancer drug products. Ex. 1005, 28; Ex. 1006, 14.



Cabozantinib is Compound IA in the '039 patent. Cabozantinib (L)-malate is Compound IB in the '039 patent and Compound (I) in Brown (Ex. 1003).

B. The '039 Patent

Exelixis faced significant challenges to make cabozantinib (L)-malate API in sufficient scale and purity for formulation into a safe, stable pharmaceutical composition suitable for human administration. *See* Ex. 1001, 3:19-34. Exelixis' initial synthetic routes included the one depicted in Scheme 1 of Brown (reproduced below, annotated with compound numbers used during the MSN litigation). Ex. 1013, ¶46; Ex. 1026, 45 (¶5).

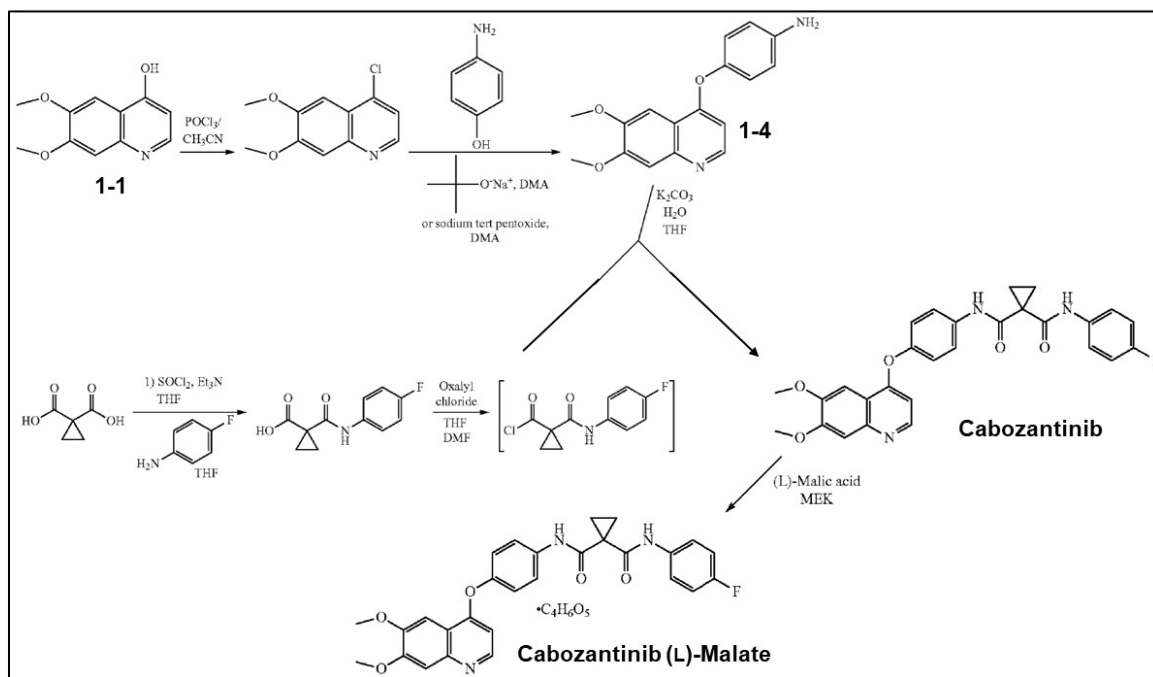


Exelixis later discovered those initial synthetic routes produced API with elevated levels of impurities and degradation products, including 6,7-dimethoxyquinoline-4-ol—the “1-1” compound (*see* Brown Scheme 1, top left).

See Ex. 1018, 42; Ex. 1013, ¶¶47-48. Exelixis found 6,7-dimethoxy-quinoline-4-ol levels up to 600 parts per million (ppm) in certain finished batches, which was significant because Exelixis discovered the compound to be genotoxic. *See* Ex. 1018, 42; Ex. 1013, ¶¶48, 50.

Exelixis discovered 6,7-dimethoxy-quinoline-4-ol formed as a degradation product during synthesis, including from decomposition of the 1-3 intermediate in the Brown process and during formation of the malate salt. Ex. 1013, ¶49; Ex. 2002, 693:3-695:10; Ex. 1026, 46 (¶8). Exelixis also discovered 6,7-dimethoxy-quinoline-4-ol could form as a degradation product upon API exposure to heat, water, oxygen, or excipients during manufacturing, and during storage of the final formulated drug product. *See* Ex. 1013, ¶52; Ex. 1018, 42-43; Ex. 1026, 46 (¶15); Ex. 2002, 600:8-15. Therefore, Exelixis determined “it was critical to essentially eliminate the impurity from the ultimate drug formulation” by ensuring “the lowest levels possible [of 6,7-dimethoxy-quinoline-4-ol] in the API.” Ex. 1013, ¶52; Ex. 2002, 605:19-606:5.

To achieve the lowest possible levels of 6,7-dimethoxy-quinoline-4-ol, Exelixis developed a new synthetic process, exemplified in the '039 patent. *See* Ex. 1001, Figure 1; Ex. 1013, ¶¶53-54. That process is reproduced below (annotated as above).



Notably, there was no easy or predictable fix to the 6,7-dimethoxy-quinoline-4-ol formation problem (which itself was not identified in the prior art), like adding a purification step or swapping out a single reaction sequence (contrary to the allegations of the district court defendant, MSN, and Petitioner, respectively). *See* Ex. 2002, 693:14-19, 694:13-695:6 (discussing numerous process changes Exelixis tried for reducing 6,7-dimethoxy-quinoline-4-ol). As the district court recognized in the MSN litigation, any process change a POSA might have made could have increased 6,7-dimethoxy-quinoline-4-ol. *See* Ex. 1026, 46 (¶¶12-13) (finding, e.g., “[r]ecrystallization would not have worked to purify the

API of the 1-1 impurity ... [and] could also produce more 1-1 impurity through ‘decomposition’”).

Exelixis spent eight years making significant process changes that spanned multiple synthetic routes, including (among others) eliminating the 1-3 intermediate in the Brown process that degrades to 6,7-dimethoxy-quinoline-4-ol, which required changing several reagents, and modifying the reaction conditions and solvent for malate salt formation. Ex. 1013, ¶54; Ex. 1018, 43; Ex. 2002, 358:10-16, 601:21-602:15, 693:14-19, 694:13-695:6. As Exelixis’ expert Dr. David MacMillan testified, Exelixis developed a process that has “a different number of steps, [which] means you have to have different chemistries involved and you have to have different molecules involved.” Ex. 2002, 673:1-674:25.

With these process changes, Exelixis was able to consistently produce a cabozantinib (L)-malate composition comprising at or below 100 ppm of 6,7-dimethoxy-quinoline-4-ol using a variety of excipients and formulation methods, even upon exposure to heat and humidity. *See* Ex. 1013, ¶57; Ex. 2012, 231-232; Ex. 1018, 43-44.

The ’039 patent describes and claims Exelixis’ invention of a cabozantinib (L)-malate composition with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. For example, it teaches that “[m]inimizing the concentration of contaminants or

byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.” Ex. 1001, 22:11-30; *see also* Ex. 2002, 686:24-687:9; Ex. 1018, 44. It describes Exelixis’ improved synthetic process, cabozantinib (L)-malate pharmaceutical compositions meeting the claimed purity limitations, and specific tablet and capsule formulations. Ex. 1001, 3:35-40, 4:6-7:42, 21:40-22:54, 24:31-31:3 (Figure 1 and Example), 31:4-32:14; *see also* Ex. 1018, 44. These teachings inform a POSA how to prepare cabozantinib (L)-malate and formulate it with a variety of excipients while maintaining 6,7-dimethoxy-quinoline-4-ol levels of 100 ppm or less. *See* Ex. 1013, ¶¶55, 57; Ex. 1018, 44.

C. Petitioner’s Positions Were Litigated

Before the ’039 patent issued, the crux of Petitioner’s grounds was rejected in the MSN litigation of the ’039 patent’s ancestor, U.S. Patent No. 11,298,349 (the “’349 patent”) (Ex. 1046). Petitioner then challenged the ’349 patent in a separate IPR petition. *See Azurity Pharms., Inc. v. Exelixis, Inc.*, IPR2025-00210, Paper 2 (P.T.A.B. Nov. 18, 2024). Institution of that petition was denied on the merits on June 4, 2025. *See* IPR2025-00210, Paper 11 (P.T.A.B. June 4, 2025).

The MSN litigation lasted two years, culminating in a three-day trial with over twelve hours of testimony relating to the ’349 patent. *See* Ex. 2001, 1:12; Ex.

2004, 1:12. The district court carefully considered *all* documentary evidence and testimony (not just the parts selectively highlighted by Petitioner) and issued a detailed opinion finding claim 3 of the '349 patent (the only claim tried) not invalid. *See* Ex. 1026. That opinion is currently under appeal to the Federal Circuit. *See Exelixis, Inc. v. MSN Labs. Private Ltd.*, No. 25-1236 (Fed. Cir.).

Petitioner cannot deny the relevance of the MSN litigation. Not only does Petitioner rely on the district court record in attempting to support the grounds of its Petition, but Petitioner also relies on Exelixis' POSA definition for the '349 patent, which Petitioner adopted in the present IPR “[g]iven the *similarity in claim language*” between the '349 and '039 patents. Pet. 12.¹ Notably, the '349 patent claim 3 at issue in the MSN litigation requires a cabozantinib (L)-malate composition “essentially free of” (i.e., admixed with 200 ppm or less of) the 6,7-dimethoxy-quinoline-4-ol impurity, and the challenged claims of the '039 patent also require a cabozantinib (L)-malate composition with low levels of the 6,7-dimethoxy-quinoline-4-ol impurity, though reduced even further to 100 ppm or less.

The district court defendants (MSN) alleged (1) “the Brown process inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1

¹ Hereinafter, all emphasis is added unless otherwise noted.

impurity”; and (2) “it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity.” Ex. 1026, 48.

The court also considered Robinson. Defendants’ experts, Drs. Maureen Donovan and Salvatore Lepore, testified that a POSA would have known from Robinson that genotoxic impurities should be maintained at low ppm levels, and that there were known methods, like recrystallization, to bring those impurities to the requisite levels. Ex. 2001, 264:17-266:19, 301:9-303:23, 310:8-311:3 (Lepore); Ex. 2002, 383:19-384:21 (Donovan).

The court found the defendants “failed to offer clear and convincing evidence that if the Brown process is followed, it will inherently result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity.” Ex. 1026, 49. The court acknowledged expert testimony from Dr. MacMillan “that a POSA would not expect any 1-1 impurity to be left at the end of Brown, because each of the five steps of Brown has a purification component and the reagents added through the process could purge the impurity,” but found that “what a POSA would have expected is not sufficient to show inherency, given that Exelixis presented evidence that the 1-1 impurity did form as a degradation product during the Brown process.” *Id.*, 50-51 n.14. Moreover, the court found a POSA would

not have been motivated to modify Brown to minimize 6,7-dimethoxy-quinoline-4-ol, crediting Exelixis' expert Dr. Allan Myerson's testimony that a "POSA would think there is, at most, a de minimis amount of impurity left after the Brown process." Ex. 1026, 53-56. Furthermore, the court found a POSA would not have been motivated "to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity," and a "POSA would not know there might be some 1-1 impurity left at the end of the Brown process." *Id.*, 55.

The district court also considered Dr. Myerson's statements "regarding the potential genotoxicity of 6,7-dimethoxy-quinoline-4-ol" referenced by Petitioner. Pet. 66. While Dr. Myerson testified on cross-examination that identification of potentially genotoxic impurities through structural alerts was known, and that a quinoline would have given such an alert, he also testified that one would have to perform an experimental Ames test to know whether a particular compound is genotoxic. Ex. 2003, 765:20-772:8 (Myerson).

The court considered this testimony but, despite finding a POSA would have determined 6,7-dimethoxy-quinoline-4-ol was a genotoxic impurity subject to regulatory guidance, further found that a POSA would not have been motivated to control for 6,7-dimethoxy-quinoline-4-ol. Ex. 1026, 45 (¶4), 46 (¶14).

As Exelixis' explained in more detail in its brief arguing for discretionary denial, Discretionary Denial Br. (Paper 8) at 7-25, Petitioner's challenge is effectively a collateral attack on the prior district court decision, now on appeal, and does not merit institution.

The Board also recently denied institution on the merits of Petitioner's parallel petition challenging the related '349 patent, the claims of which recite a less stringent purity limitation (200 ppm or less). IPR2025-00210, Paper 11 (P.T.A.B. June 4, 2025). That petition raised, *inter alia*, obviousness arguments substantially similar to the obviousness grounds raised in this Petition. *Id.*, 19-22 (summarizing Petitioner's obviousness arguments involving (1) regulatory guidance and (2) inherency in a Brown-Kubo synthesis).

In denying institution, the Board concluded Petitioner had not shown a reasonable likelihood of prevailing on the merits of its obviousness challenge. For example, the Board found that "Petitioner identifies no teaching in the prior art providing any reason to reduce levels of 6,7-dimethoxy-quinoline-4-ol specifically," that "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," that "Petitioner provides no persuasive evidence or explanation of [regulatory guidance] that suggests otherwise," and that "there would have been no

motivation to purify the composition in order to remove 6,7-dimethoxy-quinoline-4-ol.” *Id.*, 24-26.

The Board further concluded that “Petitioner has not shown that the combination of Brown, Kubo, and Remington would inherently result in less than 200 ppm impurity,” that “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,” and that Petitioner’s argument that a POSA would have expected the proposed modification to the Brown process based on Kubo to decrease the level of 6,7-dimethoxy-quinoline-4-ol failed to satisfy the high standard required for showing inherency. *Id.*, 26-29.

The grounds of the present Petition are deficient for at least the same reasons.

III. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner agrees with Petitioner’s POSA definition, Pet. 12, which is the same definition Patent Owner proposed in the MSN litigation. Ex. 1010, ¶11.

IV. CLAIM CONSTRUCTION

Patent Owner reserves the right to seek construction of one or more claim terms at a later stage in this proceeding, should the Board institute trial.

V. PETITIONER IS NOT REASONABLY LIKELY TO PREVAIL ON EITHER GROUND

Institution should be denied because Petitioner has not established a reasonable likelihood of prevailing on either ground. 35 U.S.C. § 314(a). Both grounds rely on the same primary prior art reference, Brown, that was overcome before the Office in prosecution of the challenged claims and related patents and was found not to invalidate claim 3 of the '349 patent in the MSN litigation. The references Petitioner seeks to combine with Brown—Kubo in Ground I, Robinson in Ground II—cannot fill the gaps to establish a reasonable likelihood of unpatentability. For both grounds, Petitioner misleadingly repackages testimony and findings from the MSN litigation in an attempt to support its proposed combinations, but Petitioner fails to demonstrate a reasonable likelihood of prevailing on either ground.²

² Each challenged claim recites a purity limitation of 100 ppm or less, or even lower: 50 ppm or less, 25 ppm or less, 10 ppm or less, or 5 ppm or less. Claims 6-22, which additionally recite treating cancer by administering the claimed pharmaceutical compositions, similarly recite a purity limitation of 100 ppm or less, 50 ppm or less, 25 ppm or less, 10 ppm or less, or 5 ppm or less. For at least

As Exelixis explained in more detail in its brief arguing for discretionary denial, both the district court and the USPTO repeatedly found these or related claims patentable over Brown, Kubo, and genotoxic guidance references, as well as MSN's Post-Trial Brief. Paper 8; Ex. 2014, 19-31. Not only do the similarities of the prior challenges to the grounds in this Petition make reconsidering those arguments a poor use of the Board's resources, but the repeated failure of those challenges demonstrates their fundamental weaknesses.

A. Ground I: Petitioner Has Not Shown Obviousness Over Brown In View Of Kubo

Petitioner has not demonstrated a reasonable likelihood of prevailing on obviousness over Brown and Kubo. Petitioner relies on the synthesis for cabozantinib (L)-malate in Brown, the same prior art considered by the district court in the MSN litigation, with modifications based on Kubo. In proposing this combination, Petitioner does not argue that a POSA would have been motivated to

the same reasons the prior art combinations fail to render obvious a purity level of 100 ppm or lower, they also fail to render obvious the even more stringent purity limitations in the dependent composition claims (claims 2-5) and the method of treating cancer claims that require administering compositions with the claimed purity levels.

control for 6,7-dimethoxy-quinoline-4-ol to achieve the purity limitations of the '039 patent, but rather that a POSA would have made the combination generally to improve efficiency and the purity limitations necessarily would have resulted. This Brown-Kubo inherency theory does not remedy the deficiencies in the Brown-only arguments tried and rejected in the MSN litigation—including MSN's unsuccessful argument that a purity limitation of 200 ppm or less would have been inherent in Brown.

1. Petitioner Fails To Establish Its Combination Of Brown And Kubo Discloses Or Suggests All Claim Limitations

Petitioner does not argue that Brown and Kubo, alone or in combination, teach or suggest cabozantinib (L)-malate API containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol, let alone a pharmaceutical composition comprising cabozantinib (L)-malate with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol, or a higher degree of purity required for dependent claims. Instead, Petitioner argues it should be excused from identifying where the prior art teaches or suggests the purity limitations because the requisite purity levels would have been inherent in a modified synthesis based on Brown and Kubo. But Petitioner provides no evidence to back this argument, and therefore fails to establish obviousness. Accordingly, Ground I fails.

a. Petitioner Fails To Establish That Its Combination Of Brown And Kubo Discloses Or Suggests A Cabozantinib (L)-Malate Composition Containing 100 ppm Or Less Of 6,7-Dimethoxy-quinoline-4-ol

Brown and Kubo, alone or in combination, do not disclose 6,7-dimethoxy-quinoline-4-ol as an impurity or degradation product, let alone any compositions with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Petitioner argues Brown “suggests that 6,7-dimethoxy-quinoline-4-ol can remain as a ‘reaction impurity,’” Pet. 23, but Brown never identifies or refers to 6,7-dimethoxy-quinoline-4-ol as an impurity or degradation product in the synthesis of cabozantinib (L)-malate. Instead, Brown discloses “substantially pure” pharmaceutical compositions, where substantially pure is defined as “the crystalline form of [cabozantinib (L)-malate] referred to contains at least about 90wt.% based on the weight of such crystalline form.” Ex. 1003, [0097]. And while Brown further discloses that the “remainder of the crystalline form of [cabozantinib (L)-malate] may comprise other Form(s) of [cabozantinib (L)-malate] and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared,” Brown does not identify *any* specific “reaction impurities and/or processing impurities” that might be of concern when synthesizing cabozantinib (L)-malate. *Id.*; *see also* Ex. 2003, 708:14-20 (Dr.

Myerson testifying that Brown does not disclose 6,7-dimethoxy-quinoline-4-ol as an impurity or that it might be harmful).

Petitioner cannot establish that Brown's cabozantinib (L)-malate API satisfies the claimed purity limitations for 6,7-dimethoxy-quinoline-4-ol. Instead, Petitioner distorts the district court testimony of Exelixis' experts in the MSN litigation to argue that "Brown's cabozantinib (L)-malate ... containe[d] 'at most, de minimis' 6,7-dimethoxy-quinoline-4-ol." Pet. 24. However, Exelixis' experts made no such statement. The experts did not testify 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.³ See, e.g.,

³ The district court in the MSN litigation specifically found that the defendant MSN had *not* proven Brown "inherently result[ed] in a cabozantinib (L)-malate API essentially free of the 1-1 impurity." Ex. 1026, 49. Petitioner never acknowledges this finding, let alone disputes it, instead inaccurately suggesting Exelixis' own experts testified that Brown disclosed cabozantinib (L)-malate essentially free of 6,7-dimethoxy-quinoline-4-ol. See Pet. 24, 46.

Ex. 2002, 669:3-6 (MacMillan) (“Because of all these purification steps, these purging steps, a person of ordinary skill would not believe there would be any of this material way over here [the 6,7-dimethoxy-quinoline-4-ol starting material] ending up way down here [at the end of the reaction].”); *id.*, 669:12-14 (“Well, 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. 1026, 46 (¶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.”); Ex. 2003, 709:9-14 (Myerson) (“98 percent of the 1-1 starting material is used up at the beginning of the first step, and then there are multiple purification processes and other steps with purification processes, thus that at the end of the fifth step, we would not expect any significant amount of 1-1 to carry through. We just would expect it to be de minimis.”). Further, Petitioner never argues “de minimis” means 100 ppm or less, or any other specific purity level.

Petitioner also fails to acknowledge trial testimony from the MSN litigation regarding non-prior art information about the levels of 6,7-dimethoxy-quinoline-4-ol actually formed. *See* Pet. 24, 46; Ex. 2002, 693:11-25 (Dr. Myerson testifying that “20 percent of the 1-3 [intermediate] was decomposing to 1-1,” a problem that

persisted in the Brown process). Indeed, Exelixis discovered that 6,7-dimethoxy-quinoline-4-ol formed as a degradation product throughout the Brown process, including during formation of the 1-3 intermediate, during malate salt formation, and during drug formulation, and that the degradation was “particularly challenging to control.” Ex. 2002, 600:8-601:4, 692:23-695:6. Thus, 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. See Ex. 2002, 656:6-657:6 (Dr. MacMillan testifying that while a POSA “would not have expected to have the 1-1 impurity at the end of the Brown process,” Dr. Shah testified that “Exelixis discovered that the 1-1 impurity was [in fact] not adequately controlled by the Brown process,” and therefore “I don’t believe [a POSA] would have had a reasonable expectation of success or been able to modify [Brown] to achieve that required level of impurity.”); see also *id.*, 692:23-695:6.

Petitioner’s reliance on Kubo does not remedy the deficiencies of Brown. Petitioner contends that modifying Brown with Kubo’s “one-step” approach would “further reduc[e] any amount of 6,7-dimethoxy-quinoline-4-ol in the cabozantinib (L)-malate obtained from the [Brown] synthesis” because Kubo’s approach supposedly “separate[s] any 6,7-dimethoxy-quinoline-4-ol from the 4-

(aminophenoxy)quinoline intermediate.” Pet. 30-31. But while Kubo references “a decomposition product of 4-chloroquinazoline” in its synthesis of 4-(aminophenoxy)quinoline/quinazoline derivatives, Ex. 1028, 13:1-4, Kubo never identifies 6,7-dimethoxy-quinoline-4-ol (or, indeed, any quinoline) as that decomposition product. Moreover, Petitioner does not even identify the specific reaction conditions or solvent systems under which Kubo’s generally disclosed approach allegedly would need to be performed to achieve the claimed purity levels, rendering Petitioner’s argument that Kubo’s “one-step” approach would “further reduc[e] any amount of 6,7-dimethoxy-quinoline-4-ol” conclusory and insufficient. Pet. 30-31.

Petitioner’s general combination of Kubo and Brown does not teach or suggest a cabozantinib (L)-malate composition with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Notably, Petitioner wrongly assumes Kubo’s “one-step approach is the only transformative difference between Brown’s approach to synthesizing cabozantinib (L)-malate and the ’039 patent’s approach.” Pet. 32. As described in the district court trial testimony in the MSN litigation, Exelixis made numerous, significant changes to the Brown process—over an eight-year period—to address formation of the 6,7-dimethoxy-quinoline-4-ol impurity during synthesis of the 1-3 intermediate, malate salt formation, and drug formulation. Ex. 2002,

671:10-20. Specifically, the changes, which are reflected in the synthesis described in the '039 patent, included: (1) eliminating the 1-3 intermediate that degrades to 6,7-dimethoxy-quinoline-4-ol; (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. Ex. 1013, ¶54; Ex. 1018, 43; Ex. 2002, 693:14-19, 694:13-695:6. In other words, Exelixis developed a process that “performs different steps, involves different molecules, and results in different chemistries than the [Brown process].” Ex. 1013, ¶54 (citing Ex. 2002, 673:1-674:25). The only change Petitioner even attempts to argue is disclosed by Kubo is skipping the 1-3 intermediate by replacing 4-nitrophenol with 4-aminophenol. Despite extensive trial testimony about other important differences between Brown and the process disclosed in the '349 patent (which has the same specification and thus discloses the same process disclosed in the '039 patent), Petitioner’s proposed combination does nothing to address the additional changes to effectively minimize formation of the 6,7-dimethoxy-quinoline-4-ol degradation product in later steps.

Thus, Petitioner has not established that its combination discloses or suggests a cabozantinib (L)-malate composition with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. The only way Petitioner could supply the missing claim limitation is through inherency. But as discussed below, Petitioner's arguments that the purity limitation would have been inherent from the combination of Brown and Kubo fail to meet the high standard to show inherency.

b. Petitioner Fails To Establish Inherency Of The Purity Limitations

Petitioner argues that the purity limitations would have been inherent, asserting that the requisite purity "could be" achieved using "known techniques" in a modified synthesis based on Brown and Kubo. Pet. 34-35. But Petitioner fails to show that Brown's process necessarily would result in 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol, or that Petitioner's Brown-Kubo process necessarily would do so. On Petitioner's Brown-Kubo process, 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[.]" Ex.

1043, ¶76. This is insufficient to show inherency.⁴ Notably, the Board in the parallel IPR challenging the '349 patent, addressing substantially similar arguments, agreed. *See* IPR2025-00210, Paper 11 at 27-28 (P.T.A.B. June 4, 2025).

Further, even assuming Petitioner had adequately argued motivation to combine Brown and Kubo (which it has not, *see infra* Section V.A.2), Petitioner never argues that any specific proposed pathway for synthesis of cabozantinib (L)-malate followed by formulation into a pharmaceutical composition necessarily or naturally would have resulted in a composition having the requisite purity levels, as required for inherency. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (“A party must ... meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior

⁴ Petitioner and Dr. Dichtel also fail to show that a POSA would have been motivated to reduce levels of 6,7-dimethoxy-quinoline-4-ol in the Brown process. *See* IPR2025-00210, Paper 11 at 24-26 (P.T.A.B. June 4, 2025); *infra* Section V.A.2.

art.”). Indeed, Petitioner never identifies any conditions under which Kubo’s approach allegedly would be performed in combination with the Brown process to achieve the claimed purity levels. This is insufficient to show inherency of the purity limitations.

Petitioner asserts a Brown-Kubo process “must have necessarily afforded cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or any of the lesser claimed ranges),” because Kubo’s “one-step approach is the only transformative difference between Brown’s approach to synthesizing cabozantinib (L)-malate and the ’039 patent’s approach.” Pet. 32. But as discussed above, the synthesis disclosed in the ’039 patent, which results in a highly pure cabozantinib (L)-malate API, was the result of numerous “significant” changes made to the Brown process to address the various steps during which the 6,7-dimethoxy-quinoline-4-ol degradation product formed. *See supra* Section V.A.1.a. Indeed, even Petitioner’s declarant acknowledges an additional change that would have been required to achieve the synthesis in the ’039 patent. Ex. 1043, ¶48 (observing that “the solvent used in the final crystallization step” is different). This concession demonstrates the fundamental inadequacy and incompleteness of Petitioner’s inherency argument. *Par Pharm.*, 773 F.3d at 1195-96.

Citing MSN litigation testimony from Exelixis' expert, Dr. Myerson, Petitioner claims Exelixis "cannot now contend" the purity limitations would not have been obvious based on the proposed Brown-Kubo combination or that a pure composition "could [not] be formulated" from the resulting API. Pet. 35. But Petitioner mischaracterizes Dr. Myerson's testimony; he never testified about any modified Brown-Kubo synthesis, let alone that such a process would *inherently* achieve a specific purity level in a pharmaceutical composition.⁵ See Ex. 2003, 773:7-24. He also did not testify that API purity alone could guarantee purity of a pharmaceutical composition; indeed, he said the opposite. See Ex. 2003, 712:19-

⁵ In addition to Petitioner's failure to equate its Brown-Kubo combination with a '039 patent process, *supra* Section V.A.1.a, Petitioner mistakenly relies on enablement to try to show inherency, see Pet. 34 ("To the extent that the '039 patent describes and *enables* the production of cabozantinib (L)-malate that satisfies the claimed impurity limitations, then Brown in view of Kubo must necessarily do so as well."). But enablement is distinct from inherency. *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 844 (Fed. Cir. 2020) ("Whether a prior art reference is enabled is a separate question from whether it discloses, expressly or inherently, the claimed limitations at issue.").

713:2 (Myerson) (“[T]he process of blending with excipients and making it into a drug product can result in increase in the 1-1 impurity. Thus, it’s possible to start with an API that’s essentially free [i.e., has 200 ppm or less of 1-1], but end up with a drug product that’s not essentially free due to the additional formation of the 1-1.”). Drs. Myerson and MacMillan both testified at length that the disclosures in the ’349 patent (which are the same as those in the ’039 patent)—including the new synthetic pathway involving multiple changes from Brown and a new recognition of the importance of controlling for 6,7-dimethoxy-quinoline-4-ol—arose from significant, non-obvious improvements at multiple points in the synthesis of the API. Petitioner’s oblique implication that the disclosures of *the ’039 patent and Dr. Myerson’s testimony* might demonstrate inherency⁶ is divorced from any specific teaching of the prior art and insufficient to meet the high standard for inherency.

⁶ Petitioner acknowledges Exelixis’ experts’ testimony that API essentially free of impurities does not necessarily provide a formulation essentially free of impurities in its separate Petition challenging the ’349 patent, *see* ’349 Pet. 14 n.2, but ignores it here.

Petitioner does not support its claim that “maintaining any of the claimed concentration ranges for the 6,7-dimethoxy-quinoline-4-ol impurity upon formulation must necessarily result from utilizing any one or more of the obvious choices of acceptable carriers.” Pet. 37. Though Petitioner cites MSN litigation testimony that cabozantinib (L)-malate is stable, Pet. 36-37 (citing Ex. 1024 at 661:9-663:11), Petitioner fails to mention that Exelixis’ expert also testified that common excipients could result in increased levels of 6,7-dimethoxy-quinoline-4-ol. *See* Ex. 2002 at 696:6-697:13 (“[A]ny mixture of the API [i.e., cabozantinib (L)-malate] and excipients generally resulted in an increase in the amount of 1-1 impurity.”).

Petitioner’s inherency theory is even weaker with respect to the dependent claims with lower ppm limits. Petitioner never explains what level of 6,7-dimethoxy-quinoline-4-ol it alleges would necessarily result from its proposed combination. Petitioner makes *no* distinction in its inherency argument for any of the dependent claims that recite a greater purity level (e.g., claim 6, which recites a purity level of 5 ppm or less), arguing that they all “would have been obvious for the reasons previously discussed.” Pet. 39. Ignoring the distinctions among the recited purity levels reinforces Petitioner’s fundamental failure to satisfy the exacting inherency standard.

2. Petitioner Does Not Demonstrate That A POSA Would Have Been Motivated to Modify Brown With Kubo For “Efficiency”

Petitioner’s generic “efficiency” argument is insufficient. Petitioner asserts a motivation to modify Brown’s process with Kubo’s to eliminate a step and “improve[] efficiency.” Pet. 27. However, Petitioner’s own evidence shows that “efficiency” is only one of many criteria by which to evaluate a synthesis; for example, a POSA also would have considered whether the synthesis is “reliable” or the “lowest risk approach” and overall yield. *See* Ex. 1029, 133; Ex. 1030, 3011. Petitioner’s proposed modification starts with the Brown process—about which Petitioner identifies no known concerns before February 2011—and introduces reactions developed for substrates different from Brown’s. Specifically, the only examples in Kubo that use the reactions relied on by Petitioner to allegedly improve efficiency and reduce impurities involved not only a different substrate from the 4-chloro-6,7-dimethoxyquinoline of Brown (4-chloro-6,7-dimethoxyquinazoline), but also a different aminophenol (4-amino-3-chlorophenol hydrochloride instead of 4-aminophenol). *See* Ex. 1028, 33:51-34:31. Whether such reactions would have worked on Brown’s 4-chloro-6,7-dimethoxyquinoline with a good yield and purity profile would have been uncertain and taken significant time and effort to implement and evaluate. Given that there were no drawbacks of Brown disclosed in the art, a POSA would not have been motivated

to modify Brown with untested reactions and risk a lower yield and/or worse impurity profile simply to “improve[] efficiency.” Pet. 27.

As part of its “efficiency” motivation argument, Petitioner asserts in a single sentence that “Kubo further teaches that the one-step approach can simplify product isolation and improve purity.” Pet. 29. But without any motivation to improve purity *in the Brown process* (which the Petition neither argues nor provides evidence to support)⁷, this generic possibility of potentially “improv[ing] purity” with Kubo would not provide a motivation to depart from Brown’s established synthesis. Petitioner’s theory is based on improper hindsight and fails to show the claims would have been obvious at the time of the invention. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (rejecting obviousness theory that “simply retraced the path of the inventor with hindsight [and] discounted the number and complexity of the alternatives” because

⁷ The Board in the parallel IPR challenging the ’349 patent, considering substantially similar arguments and evidence, found that “Petitioner identifies no teaching in the prior art providing any reason to reduce levels of 6,7-dimethoxyquinoline-4-ol specifically.” See IPR2025-00210, Paper 11 at 24 (P.T.A.B. Jun. 4, 2025).

“at the time of invention, the inventor’s insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted”).

B. Ground II: Petitioner Has Not Shown Obviousness Over Brown In View Of Robinson

Petitioner has not demonstrated a reasonable likelihood of prevailing on obviousness over Brown and Robinson. Petitioner relies on the same primary reference, Brown, as relied on in Ground I, but in view of a different secondary reference, Robinson. The deficiencies in Brown are not remedied by Robinson either.

1. Petitioner Fails To Establish Its Combination Of Brown And Robinson Discloses Or Suggests All Claim Limitations

Petitioner’s Ground II argument rests on the fundamentally flawed premise that Brown’s process resulted in “a ‘de minimis’ amount of 6,7-dimethoxy-quinoline-4-ol,” Pet. 50, but that a POSA nonetheless would have been motivated by generic regulatory guidance to reduce its level to the purity levels in the challenged claims. As explained above for Ground I, *supra* Section V.A.1.a, Brown does not disclose or suggest that 6,7-dimethoxy-quinoline-4-ol was an expected degradation product of its synthetic pathway.

Nevertheless, Petitioner asserts that “6,7-dimethoxy-quinoline-4-ol was the starting material and an expected degradant of an intermediate in Brown’s

synthesis.” Pet. 50. But that argument is belied by Petitioner’s reliance on trial testimony from the MSN litigation that a POSA would in fact have expected only “de minimis” amounts of 6,7-dimethoxy-quinoline-4-ol. Pet. 50 (citing Ex. 1019 at 708:23-709:19). The trial testimony on which Petitioner relies explains that at most “de minimis” amounts of 6,7-dimethoxy-quinoline-4-ol would have been expected precisely because it was not known to be a degradation product in the Brown process. Pet. 50; Ex. 1019, 708:23-709:19. Petitioner is also incorrect that “[i]t is of no moment that Brown does not expressly report [6,7-dimethoxy-quinoline-4-ol’s] presence or absence in the synthesized cabozantinib (L)-malate.” Pet. 50. Brown’s complete silence on this point is further evidence that 6,7-dimethoxy-quinoline-4-ol was not known to be a degradation product of the synthesis.

Robinson does not remedy the deficiencies of Brown. Robinson merely provides general background about regulatory guidance to reduce impurities known to be actually or potentially genotoxic and describes some common techniques for controlling impurities in drug substances generally. For example, the only disclosure Petitioner cites in Robinson for supposedly teaching the need to control 6,7-dimethoxy-quinoline-4-ol levels in Brown’s process is that “[a] drug substance will typically contain a range of low-level impurity compounds, for

example arising as *residues of starting materials*, reagents, intermediates, or as *side-products generated by the synthetic processes or degradation reactions....*”

Pet. 50 (quoting Ex. 1039, 946) (emphasis in original). Robinson goes on to state generically that “these need to be understood and controlled within tight limits.”

Ex. 1039, 946.

Robinson does not teach or suggest any specific steps or approaches to control for 6,7-dimethoxy-quinoline-4-ol specifically, and certainly not in the context of an API where a POSA would not have even expected any appreciable amount of 6,7-dimethoxy-quinoline-4-ol to be present. Robinson similarly does not teach or suggest any specific reason to test for or identify 6,7-dimethoxy-quinoline-4-ol as a degradation product in the Brown process.

The implication of Petitioner’s Ground II argument is that *any* purity limitation for *any* potential genotoxic impurity, whether known or unknown at the time, for *any* pharmaceutical composition would have been obvious based merely on generic regulatory guidance that requires testing for and minimizing genotoxic impurities. This argument trivializes the challenges and effort actually required to develop effective and safe pharmaceutical compositions. Indeed, as explained above, *see supra* Section II.B, it took Exelixis eight years and numerous substantial changes to the Brown synthesis to be able to control 6,7-dimethoxy-quinoline-4-ol

once it had been identified as a genotoxic degradation product. Robinson, itself, acknowledges that attaining low impurity levels “can require the deployment of significant resources,” Ex. 1039 at 950, which undercuts Petitioner’s argument that a POSA would have expected success in controlling for impurities because, generally, “[t]he pharmaceutical industry was already successfully following the regulatory authorities’ recommendations” about impurity levels, Pet. 55. Indeed, Robinson acknowledges that not all genotoxic impurities can be controlled: The EMEA decision tree demonstrates that for drugs in which the level of a genotoxic impurity is “as low as reasonably practicable” but the intake level exceeds the “threshold of toxicological concern” (i.e., the “levels of contamination where the risk of harm is negligible”) and such intake is unacceptable, the use of that drug must be restricted or rejected. Ex. 1039, 947, 948 (Figure 1).

2. Petitioner Fails To Establish A Motivation To Modify Brown With Preparative Chromatography As Disclosed In Robinson

As discussed above, Petitioner does not demonstrate any expectation that 6,7-dimethoxy-quinoline-4-ol would have been forming in the Brown process. *See supra* Section V.B.1. Without any expectation that 6,7-dimethoxy-quinoline-4-ol would have been forming, there would have been no motivation to purify cabozantinib (L)-malate to remove 6,7-dimethoxy-quinoline-4-ol or otherwise

control for 6,7-dimethoxy-quinoline-4-ol in the synthetic process, API, or formulation.⁸

Even if Petitioner were correct that generic regulatory guidance offered some motivation to test for and reduce impurities, Petitioner fails to demonstrate a motivation to use preparative chromatography, including the specific preparative chromatography method Petitioner selects from Robinson and Maddula.

Robinson identifies four broad “industry approaches” to address potentially genotoxic impurities: (1) altering the synthesis so as to remove the potentially genotoxic impurity entirely; (2) adjusting process parameters to reduce the

⁸ As the Board acknowledged in rejecting Petitioner’s regulatory guidance argument in the parallel IPR challenging the related ’349 patent, “knowing contamination is present is critical to the motivation to purify.” IPR2025-00210, Paper 11 at 25 (P.T.A.B. June 4, 2025); *see also* Ex. 2002, 669:12-14 (MacMillan) (“[I]f 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.”). Accordingly, the Board concluded that “there would have been no motivation to purify the composition in order to remove 6,7-dimethoxy-quinoline-4-ol.” IPR2025-00210, Paper 11 at 25 (P.T.A.B. June 4, 2025).

potentially genotoxic impurity to below a level of concern; (3) deploying chemical and mechanistic arguments to demonstrate that the potentially genotoxic impurity will not be present at significant levels; and (4) conducting testing to demonstrate that the potentially genotoxic impurity is not actually harmful at its typical level in the API. Ex. 1039, 952. Within each industry approach, Robinson identifies multiple examples of more specific techniques. *Id.*, 952-959. Within the adjusting process parameters approach, Robinson states, among other examples, that Maddula's preparative chromatography method might be appropriate for "an extreme case." Ex. 1039 at 955.

Petitioner never explains why a POSA would have been motivated to choose this specific industry approach (i.e., adjusting process parameters) over the three other industry approaches discussed in Robinson, to address the challenge of minimizing 6,7-dimethoxy-quinoline-4-ol in cabozantinib (L)-malate. Petitioner also never explains why a POSA would have been motivated to choose preparative chromatography, let alone Maddula's specific preparative chromatography method, from among the various examples discussed in Robinson by which a POSA could have adjusted process parameters, to address the challenge of minimizing 6,7-dimethoxy-quinoline-4-ol in cabozantinib (L)-malate. Rather, Petitioner argues only that preparative chromatography "was a known solution." Pet. 55. Robinson

discloses numerous process techniques other than Maddula's preparative chromatography method, and Maddula acknowledges there are "scant reports" of using its specific method to produce active pharmaceutical ingredients. Ex, 1049, 685.

It is hindsight for Petitioner to pick out preparative chromatography, let alone the specific preparative chromatography method of Maddula, from the laundry list of possible options mentioned in Robinson.

But even if one were to set aside the other industry approaches and process techniques discussed in Robinson, Petitioner fails to show why a POSA would have been motivated to use preparative chromatography in attempt to obtain a cabozantinib (L)-malate composition containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. According to Petitioner's declarant, Dr. Dichtel, chromatography would "purify[] cabozantinib (L)-malate API from 6,7-dimethoxy-quinoline-4-ol to the levels recited in claims 1-10." Ex. 1043, ¶112. But Petitioner assumes the output of preparative chromatography would be the (L)-malate salt; however, Petitioner has neither explained why this would be the case nor identified an example where subjecting a salt to preparative chromatography yields that salt back. The only example cited by Petitioner is Maddula, which did not use preparative chromatography to purify a salt. *See* Ex. 1049, 683 (Figure 1).

Contrary to Petitioner's apparent assumption, subjecting cabozantinib (L)-malate to preparative chromatography would cause cabozantinib to dissociate from (L)-malate, meaning that the output from preparative chromatography would be cabozantinib free base, not the (L)-malate salt of cabozantinib. Consequently, performing Petitioner's purported purification method to separate 6,7-dimethoxyquinoline-4-ol from cabozantinib (L)-malate would require a POSA to isolate cabozantinib free base after the proposed chromatography and then remake the (L)-malate salt—all before even attempting to formulate it. This would not have motivated a POSA to use preparative chromatography for at least two reasons.

First, (L)-malate salt formation is a source of degradation to form 6,7-dimethoxyquinoline-4-ol. *See, e.g.*, Ex. 1026, 45 (¶2), 46 (¶15); Ex. 2002, 600:10-15, 689:17-690:4, 694:25-695:10; 697:14-21, 700:10-19. Petitioner fails to show why a POSA would have sought to develop and implement a purification method that necessitates a step that could reintroduce 6,7-dimethoxyquinoline-4-ol.

Second, Petitioner fails to show why a POSA would have been motivated to prepare the (L)-malate salt of cabozantinib according to the Brown process, only to then eliminate that salt via preparative chromatography. Both Petitioner and Dr. Dichtel contend that a POSA would have expected that chromatography could be used to purify cabozantinib (L)-malate to the claimed levels. Pet. 55-57; Ex. 1043,

¶112. But Petitioner overlooks that any purportedly “pure” cabozantinib resulting from chromatography would be the free base, and would then have to be re-subjected to (L)-malate salt formation, thereby adding an additional step to the Brown process, followed by formulation into a pharmaceutical composition—two processes where degradation to form 6,7-dimethoxyquinoline-4-ol can occur. *See, e.g.*, Ex. 1026, 45 (¶2), 46 (¶15); Ex. 2002, 600:10-15, 689:17-690:4, 694:25-695:10, 697:14-21, 700:13-17. This also highlights the selective and hindsight-driven nature of Petitioner’s arguments. On the one hand, Petitioner argues that a POSA would have modified Brown with Kubo to eliminate a synthetic step and thereby promote efficiency. *See supra* Section V.A.2. But here, Petitioner argues that a POSA would have implemented a chromatography method that ***adds*** two steps (chromatography and salt re-formation) to the Brown process.

Thus, Petitioner fails to show why a POSA would have been motivated to use a purification approach that does not even yield cabozantinib (L)-malate, let alone a composition of cabozantinib (L)-malate, containing 100 ppm or less of 6,7-dimethoxyquinoline-4-ol, and that would have required additional steps that could have reintroduced the very impurity sought to be eliminated.

3. Petitioner Fails To Establish A Reasonable Expectation Of Success In Modifying Brown With Preparative Chromatography As Disclosed In Robinson

Petitioner fails to demonstrate a reasonable expectation of success in achieving the claimed purity limitations using the Brown process along with generic regulatory guidance and preparative chromatography, including the specific preparative chromatography method mentioned briefly in Robinson.

First, Petitioner is incorrect that there would have been a reasonable expectation of success in using preparative chromatography to achieve a cabozantinib (L)-malate composition containing 100 ppm or less of 6,7-dimethoxyquinoline-4-ol simply because Brown already used a different type of chromatography step for a different purpose, at a different stage in the synthesis. *See* Pet. 57. Brown used “in process high-performance liquid chromatography” (HPLC) to monitor the consumption of the starting 6,7-dimethoxyquinoline-4-ol in the reaction to form 4-chloro-6,7-dimethoxyquinoline. *See* Ex. 1003, [00102]. Petitioner never explains why Brown’s use of in-process HPLC to *monitor* reaction of compounds that do not include cabozantinib, let alone a salt of cabozantinib, would have provided a POSA any reasonable expectation of success in using preparative chromatography (let alone Maddula’s specific preparative chromatography) to *purify* cabozantinib (L)-malate.

Second, contrary to Petitioner’s assertion that “[i]t would be reasonable to expect that chromatography could be used to purify *cabozantinib (L)-malate* to within the claimed concentration ranges,” Pet. 57, a POSA would not have reasonably expected performing chromatography on cabozantinib (L)-malate to yield cabozantinib (L)-malate, let alone a composition of cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. As explained above, *see supra* Section V.B.2, subjecting cabozantinib (L)-malate to preparative chromatography would result in dissociation of the salt to yield cabozantinib free base, requiring reperforming the salt formation step to re-create cabozantinib (L)-malate salt and then formulating it into the composition—processes where degradation to form 6,7-dimethoxyquinoline-4-ol can occur. *See, e.g.*, Ex. 1026, 45 (¶2), 46 (¶15); Ex. 2002, 600:10-15, 689:17-690:4, 694:25-695:10; 697:14-21, 700:13-17.

Third, Maddula explains that it can be difficult to eliminate impurities in some drug products, and that, for its preparative chromatography method to be successful, a number of variables need to be considered and optimized, none of which Petitioner discusses. *See* Ex. 1049 at 683 (“In some cases, it is nearly impossible to eradicate impurities from drugs that impose a great challenge.”); *id.* at 689 (summarizing variables that must be considered and optimized); *id.* at 685

(noting “[t]here are scant reports” regarding aspects of hydrophobic interaction chromatography for “preparative LC for industrial production of active pharmaceutical ingredients (API)”). For example, Robinson explains that Maddula applied its “understanding [of] the physicochemical properties of the API, impurity, and adsorbent material” to design/develop “a negative hydrophobic interaction chromatographic process for removal of the genotoxic []impurity.” Ex. 1039 at 955. This demonstrates that Maddula’s purification method is highly dependent on the physicochemical properties of both the API and the impurity.

Maddula’s API is not a salt like cabozantinib (L)-malate, and both Maddula’s API and impurity are structurally distinct from cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol. *See* Ex. 1043, ¶116 (“Admittedly, cabozantinib (L)-malate and 6,7-dimethoxyquinoline-4-ol are not the same API and structurally related impurity that Maddula successfully removed using preparative chromatography.”). Petitioner’s argument that the differences between cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol from the API and impurity studied in Maddula “would not negate the reasonable expectation of success afforded by either Robinson or Maddula,” Pet. 56, is conclusory and wrong. The burden is on Petitioner to show that there would have been a reasonable expectation of success with the proposed combination. Here that means

explaining why Maddula’s method—that was only successfully performed on a *different* API and *different* impurity and highly dependent on the physicochemical properties of both the API and the impurity—also would have been expected to afford the claimed purity levels with respect to cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol.

Petitioner cites *Pfizer Inc. v. Sanofi Pasteur Inc.* for the proposition that “a prior art reference is not limited to its specific working examples” to suggest that Maddula’s method would be applicable to the separation of 6,7-dimethoxy-quinoline-4-ol from cabozantinib (L)-malate. Pet. 56-57 (citing 94 F.4th 1341, 1349 (Fed. Cir. 2024)). Petitioner’s reliance on *Pfizer* is misplaced. *Pfizer* addressed whether prior art references that disclosed but did not exemplify certain limitations would have rendered those limitations obvious. *Pfizer*, 94 F.4th at 1349. Maddula, by contrast, neither discloses nor suggests separating 6,7-dimethoxy-quinoline-4-ol from any API, let alone cabozantinib (L)-malate.

Likewise, Petitioner’s reliance on *Par Pharmaceutical* for the proposition that “technology of general applicability afforded a reasonable expectation of success” is misplaced. Pet. 57 (citing 773 F.3d at 1198). While the court in *Par Pharmaceutical* found that there would have been a reasonable expectation of success in using a particular nanoparticle technology, the court explained that the

prior art (1) “made clear that the use of nanoparticle technology in formulation chemistry had become fairly reliable and showed consistent results regarding bioavailability, viscosity, and interpatient variability”; (2) “discussed the successful use of nanoparticle technology” with other drugs in the same class as the drug at issue; and (3) “identified that one of the key benefits of the nanoparticle technology was its simplicity.” *Par Pharm.*, 773 F.3d at 1198. Petitioner has not shown that any of these reasons applies in the context of a proposed preparative chromatography step (let alone Maddula’s specific preparative chromatography process) for cabozantinib (L)-malate.

Contrary to Petitioner’s argument, the proper question is not whether the differences between Maddula’s API and impurity compared to cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol “negate” the reasonable expectation of success, Pet. 56, but rather whether Petitioner has demonstrated a reasonable expectation of success in applying Maddula’s technique in an entirely different context. Petitioner merely asserts that preparative chromatography also would have worked for cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol, providing only a conclusory explanation for why that allegedly would have been expected to be the case. Pet. 56-57. Petitioner’s declarant Dr. Dichtel contends that “Maddula and the observed results merely serve to provide a reasonable

expectation that *preparative chromatography* can be used to reduce the concentration of an impurity such as 6,7-dimethoxy-quinoline-4-ol” because “[s]ystematic methods to develop the parameters for preparative chromatography are generally known.” Ex. 1043, ¶116. However, neither Maddula nor Robinson suggests that “preparative chromatography” as a general technique would effectively control a genotoxic impurity in general, let alone 6,7-dimethoxy-quinoline-4-ol in particular. Indeed, Maddula’s low-pressure negative hydrophobic interaction liquid chromatography method was developed specifically for the API and impurity at issue in Maddula when other purification approaches failed. Neither Robinson nor Maddula suggests that this specific purification method would be broadly applicable to any API and impurity. Rather Maddula says this is a specific solution to a specific problem. *See* Ex. 1049, 689 (“Therefore, *specific* separation problems may be solved by predicting physicochemical descriptors of solute and applying them to understand the selectivity and retention mechanism as well.”), 685 (“In the present work three solute molecular descriptors ... were used to develop a preparative hydrophobic LC method for removal of the *above said impurity* from *rizatriptan*”); Ex. 1043, ¶116 (Dichtel) (“Admittedly, cabozantinib (*L*)-malate and 6,7-dimethoxyquinoline-4-ol are not the same API and structurally related impurity [as in] Maddula” and “I

am not suggesting that Brown's cabozantinib (*L*)-malate be subjected to the exact procedure that Maddula developed.”).

Petitioner fails to demonstrate that Maddula's specific purification method, or any other unidentified “preparative chromatography” method, would have provided a reasonable expectation of success in achieving a cabozantinib (*L*)-malate composition having the claimed very low levels of 6,7-dimethoxy-quinoline-4-ol.

VI. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

Objective indicia of nonobviousness are not just “cumulative or confirmatory ... but constitute[] independent evidence of nonobviousness.” *Ortho-McNeil*, 520 F.3d at 1365. Here, objective indicia including commercial success, long-felt but unmet need, and unexpected results support non-obviousness. Patent Owner reserves the right to argue objective indicia later in this proceeding, should the Board institute trial.

VII. CONCLUSION

Patent Owner respectfully requests denial of institution.

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	Trial Tr. Vol. 1, Oct. 23, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2002	Trial Tr. Vol. 2, Oct. 24, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2003	Trial Tr. Vol. 3, Oct. 25, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2004	Trial Tr. Vol. 4, Oct. 26, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)
2005	<i>Reserved</i>
2006	<i>Reserved</i>
2007	<i>Reserved</i>
2008	File History (Partial) for U.S. Patent Application No. 15/348,716
2009	<i>Reserved</i>
2010	<i>Reserved</i>
2011	<i>Reserved</i>
2012	File History (Partial) for U.S. Patent Application No. 17/170,275
2013	File History (Partial) for U.S. Patent Application No. 18/436,836
2014	Defendants' Opening Post-Trial Brief on Invalidity, Dec. 12, 2023, <i>Exelixis, Inc. v. MSN Labs. Private Ltd., et al.</i> , No. 22-228-RGA (D. Del.)

Exhibit No.	Description
2015	<i>Reserved</i>
2016	Complaint, <i>Exelixis, Inc. v. Azurity Pharms., Inc. et al.</i> , No. 25-cv-00478 (D. Del. Apr. 18, 2025), D.I. 1
2017	First Amended Complaint, <i>Exelixis, Inc. v. Azurity Pharms., Inc. et al.</i> , No. 25-cv-00478 (D. Del. Apr. 24, 2025), D.I. 7
2018	Letter from Azurity Pharms., Inc. to Exelixis, Inc. Re: Notice of Paragraph IV Certification (Mar. 5, 2025), Letter and Enclosure Annexure C

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response contains 8,973 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. §42.24(d), excluding the parts exempted from the word count by 37 C.F.R. §42.24(a)(1).

By: /Emily R. Whelan/
Emily R. Whelan (Reg. No. 50,391)

CERTIFICATE OF SERVICE

I hereby certify that on June 6, 2025, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Word Count Certification Under 37 CFR §42.24(d)
- Patent Owner's Exhibit List

to be served via e-mail, as consented to by Petitioner, on the following attorneys of record:

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