

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELIXIS, INC.,
Patent Owner.

Case IPR2025-00210
Patent 11,298,349

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

The validity of U.S. Patent No. 11,298,349 (the “’349 patent”) has already been upheld in district court, and that decision is currently on appeal to the Federal Circuit. Petitioner asks the Board to revisit what the district court and Patent Office already carefully analyzed and rejected. The district court litigation involved invalidity assertions based on the same Brown reference asserted here. In seeking to repeat the trial, Petitioner ignores that the judge carefully considered the same issues and found claim 3 non-obvious.¹ Petitioner instead selectively and misleadingly presents only portions of the district court record favorable to its position and offers no argument for why the analysis for claims 1 and 2 should be any different than for claim 3. Such gamesmanship should be rejected.

History aside, denial is warranted because the Petition fails to establish a reasonable likelihood of unpatentability. The ’349 patent claims a formulation of cabozantinib (L)-malate essentially free of process byproducts or contaminants. This novel formulation resulted from Exelixis’ discovery that an impurity—6,7-dimethoxy-quinoline-4-ol—arose during manufacture of cabozantinib (L)-malate. As of the ’349 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

¹ Claim 3 was the only claim of the ’349 patent tried.

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 this impurity—ultimately resulting in the claimed formulation.

Petitioner's grounds rely on substantially the same art and arguments considered during prosecution of the '349 patent and its predecessor applications. Petitioner has not identified a material error by the Examiner. Petitioner merely disagrees with the Examiner, which is not enough to warrant institution.

In Ground I, Petitioner stretches to assert the challenged claims are not described by, but are anticipated by, their priority application ("Wilson" or "the '559 application"). Petitioner fails to explain how these positions are both simultaneously true, and Wilson is not prior art unless priority is broken. Petitioner fails to demonstrate lack of written description (or other basis) to break the priority chain—the '559 application discloses the claimed categories of excipients, specific formulations and representative examples for each category, and purity levels as claimed. The '559 application provides more than adequate written description for the challenged claims.

In Ground II, Petitioner asserts three references, Brown, Kubo, and Remington. Setting aside that the district court considered Brown and Remington and the Patent Office considered Brown, Kubo, and the substance of Remington,

Ground II fails on the merits. Petitioner proposes modifying Brown's process for making cabozantinib (L)-malate with a sequence from Kubo. But neither Brown nor Kubo discloses 6,7-dimethoxy-quinoline-4-ol as an impurity that needs to be controlled. Furthermore, Petitioner does not demonstrate that material produced by the alleged combination would be essentially free of 6,7-dimethoxy-quinoline-4-ol (inherently or otherwise), or that a pharmaceutical composition containing the material would be. Petitioner's motivation for combining Brown and Kubo is supposedly to improve efficiency, without reference to purity levels for any byproducts or contaminants. Petitioner resorts to generic regulatory guidance to identify and reduce impurities and Remington's formulation treatise to somehow achieve a composition "essentially free" of process byproducts or contaminants. The theory does not hold together: Petitioner (1) never argues its references disclose or suggest the requisite purity level in the final pharmaceutical composition, (2) never presents evidence that such purity levels would have been an inherent result of the proposed Brown-Kubo synthesis, (3) never argues motivation to combine its references to achieve the claimed purity levels, and (4) fails to establish a reasonable expectation of success.

Throughout, Petitioner and its experts contradict their own factual arguments and opinions—indeed, the factual premises for Petitioner's two grounds are incompatible. Petitioner tries to argue that preparation of pharmaceutical

compositions as claimed was both so difficult that the robust disclosure in the priority application was insufficient to describe it (Ground I) and, at the same time, obvious (Ground II).² Ultimately, Petitioner fails to articulate why the challenged claims are unpatentable under either theory.

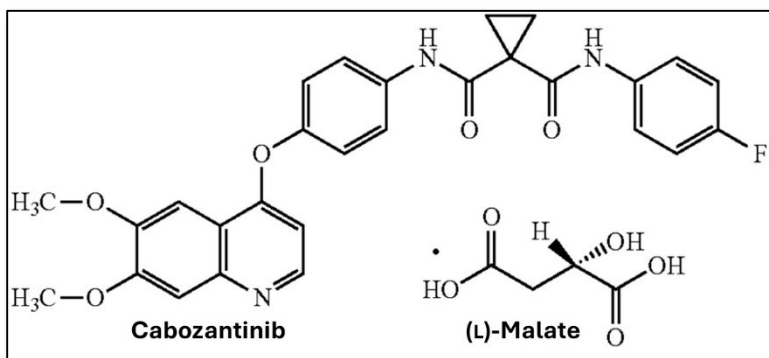
Institution should be denied.

II. BACKGROUND

A. Cabozantinib (L)-Malate

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

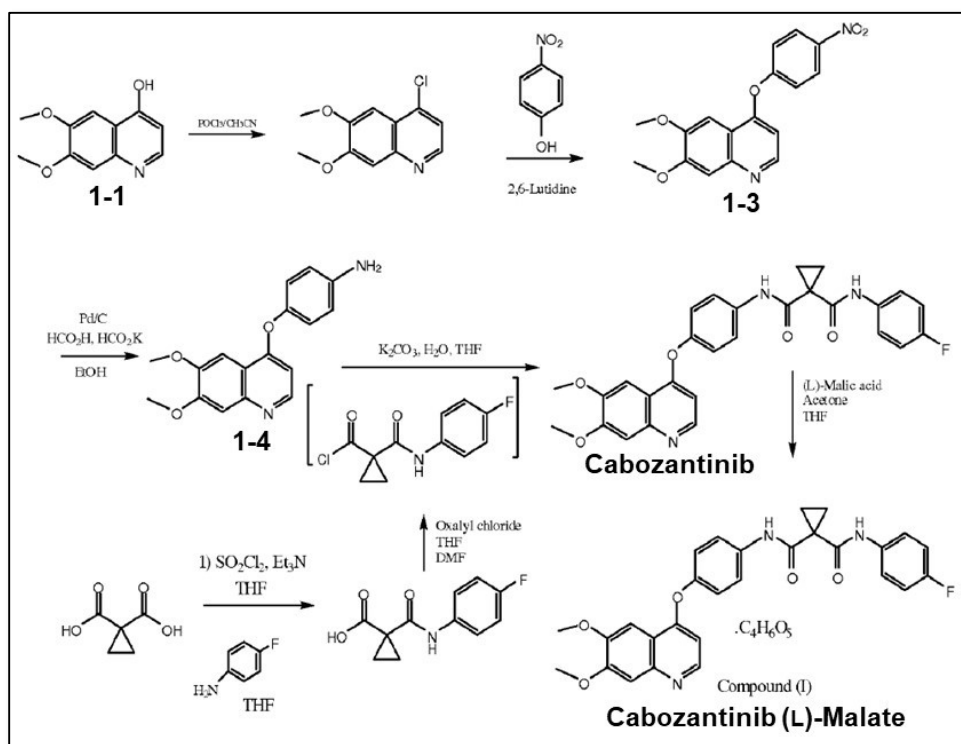
² In *Azurity Pharms., Inc. v. Exelixis, Inc.*, IPR2025-00427 (challenging U.S. Patent No. 12,128,039, a descendant of the ’349 patent, which issued October 29, 2024), Petitioner certified that the ’039 patent was eligible for IPR at the time its petition was filed (less than 9 months after issuance). That certification supports that the priority chain was not broken with the ’349 patent.



Cabozantinib is Compound IA in the '349 patent. Cabozantinib (L)-malate is Compound IB in the '349 patent and Compound (I) in Brown (Ex. 1003).

B. The '349 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 district court litigation). Ex. 1013, ¶46; Ex. 1026, 45 (¶5).

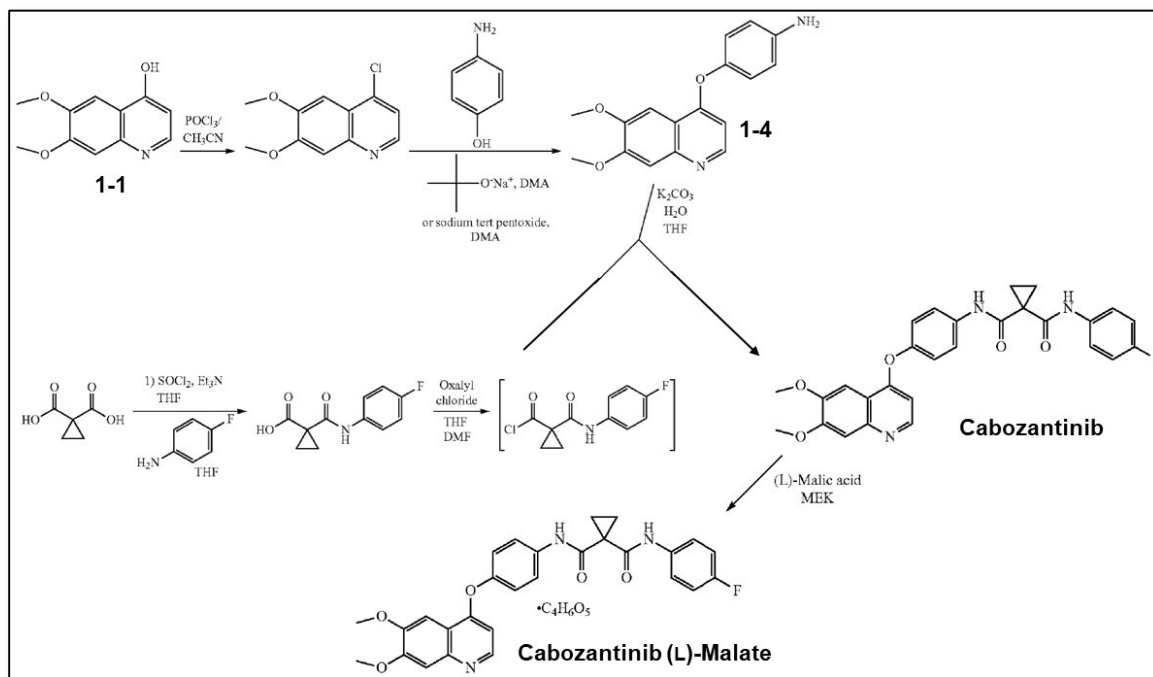


Exelixis discovered those initial synthetic routes produced API with elevated levels of impurities and degradation products, including 6,7-dimethoxyquinoline-4-ol—the “1-1” compound (*see* Brown Scheme 1, top left). *See* Ex. 1018, 42; Ex. 1013, ¶¶47-48. Exelixis found 1-1 levels up to 600 parts per million (ppm) in certain finished batches, which was significant because Exelixis discovered the compound to be genotoxic. *See* Ex. 1018, 42; Ex. 1013, ¶50.

Exelixis discovered 1-1 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 1-1 could form as a degradation product

upon API exposure to heat, water, oxygen, or excipients during manufacturing, and during storage of the final 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 1-1] in the API.” Ex. 1013, ¶52; Ex. 2002, 605:19-24.

To achieve the lowest possible levels of 1-1, Exelixis developed a new synthetic process, exemplified in the '349 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 1-1 degradation 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 and Petitioner, respectively). *See* Ex. 2002, 693:14-17, 694:13-695:6 (discussing numerous process changes Exelixis tried for reducing 1-1). As the district court recognized, any process change a POSA might have made could have increased 1-1. *See* Ex. 1026, 46 (¶¶12-13) (finding, for example, “[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 1-1, which required changing several reagents, and modifying reaction conditions and solvent for malate salt formation. Ex. 1013, ¶54; Ex. 1018, 43; Ex. 2002, 358:10-16, 601:21-602:15, 693:14-17, 694:13-695:6. In other words, Exelixis developed a process that “performs different steps, involves different molecules, and results in different chemistries.” Ex. 1013, ¶54 (citing Ex. 2002, 673:1-674:25).

With these process changes, Exelixis was able to consistently produce a cabozantinib (L)-malate composition comprising below 200 ppm of impurities, including 1-1, using a variety of excipients and formulation methods, and even upon exposure to heat and humidity. *See* Ex. 1013, ¶57; Ex. 1014, 127-128; Ex. 1018, 43-44.

The '349 patent describes and claims Exelixis' invention of a cabozantinib (L)-malate composition essentially free of impurities, including 1-1. For example, it teaches that "[m]inimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol [i.e., 1-1] in pharmaceutical compositions destined for human administration is desirable." Ex. 1001, 22:8-27; *see also* Ex. 2002, 686:24-687:9; Ex. 1018, 44. It describes Exelixis' improved process, cabozantinib (L)-malate pharmaceutical compositions meeting the claimed purity limitations, and specific tablet and capsule formulations. Ex. 1001, 3:29-34, 5:6-7:24, 21:37-22:32, 24:30-30:61 (Figure 1 and Example), 31:1-25; *see also* Ex. 1018, 44. These teachings inform a POSA how to prepare cabozantinib (L)-malate and formulate it with a variety of excipients, yet still have 1-1 levels below 200 ppm. *See* Ex. 1013, ¶¶55, 57; Ex. 1018, 44.

C. The '349 Patent Was Litigated Extensively

Litigation of the '349 patent lasted two years, culminating in a three-day trial with over twelve hours of testimony relating to the '349 patent. *See Exelixis, Inc. v. MSN Labs. Private Ltd.*, No. 22-228-RGA (D. Del.); 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), issuing a detailed opinion finding challenged claim 3 not invalid. *See* Ex. 1026. That opinion is currently under appeal to the Federal Circuit.

The district court defendants alleged (1) “the Brown process inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1 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 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.” *Id.*, 49. The court noted expert testimony from Dr. David 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.*, n.14, 50-51.

The court found a POSA would not have been motivated to modify Brown to minimize 1-1, crediting Dr. Allan Myerson’s expert testimony that a “POSA would think there is, at most, a de minimis amount of impurity left after the Brown process.” *See id.*, 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. Notably, the court found that a POSA would not have been motivated to control for 1-1 even after finding a POSA would have determined 1-1 was a genotoxic impurity subject to regulatory guidance. *See* Ex. 1026, 45 (¶4), 46 (¶14).

Petitioner’s attempt to repackage and reargue obviousness based on Brown should be denied.

III. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner agrees with Petitioner’s POSA definition, Pet. 10, which is the same definition Patent Owner proposed in district court. Ex. 1010, ¶11.

IV. CLAIM CONSTRUCTION

Patent Owner agrees with the construction of “essentially free” adopted by the district court and referenced by Petitioner, Pet. 10-11.

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 any ground. 35 U.S.C. § 314(a).

Petitioner’s two grounds fundamentally contradict each other. On the one hand, Petitioner argues a POSA would not believe the inventors possessed cabozantinib (L)-malate pharmaceutical compositions having the claimed purity— notwithstanding that the specification discloses *multiple examples* of such

compositions. At the same time, Petitioner argues a POSA would have a reasonable expectation of arriving at cabozantinib (L)-malate pharmaceutical compositions having the claimed purity—notwithstanding that the prior art contained *not a single example* of such a composition. Those two positions are irreconcilable, and the petition fails.

A. Ground I: The Challenged Claims Are Not Anticipated

Ground I argues the '349 patent's own disclosure anticipates its claims, an argument that hinges on a fatally flawed written description challenge. Petitioner argues the Wilson patent (Ex. 1002, issued from USSN 13/984,559 (the "'559 application'"))—a grandparent of the '349 patent, with an identical specification—is prior art that anticipates the challenged claims, yet supposedly does not provide written description for the challenged claims so the priority chain is broken. Pet. 20-30. Specifically, Petitioner's written description challenge turns on whether the '559 application supports the claimed categories of excipients in pharmaceutical

compositions essentially free of impurities. Pet. 13-14; 22. Unless priority is broken, Wilson is not prior art and cannot anticipate.³

As an initial matter, Petitioner has not identified any procedural break in the '349 patent's priority chain. *See* Ex. 1001, 1:9-23. In accordance with 35 U.S.C. § 120, the application leading to the '349 patent was timely filed during the pendency of its parent application, and likewise, the other applications in the priority chain were timely filed during the pendency of the immediately preceding application. Ex. 1014, 4; Ex. 2005, 23; Ex. 2006, 78; Ex. 2007, 208; Ex. 2008, 197; Ex. 2009, 302; Ex. 2010, 3-4. Further, the '349 patent and its predecessors each include a specific reference to all prior applications in the priority chain, identifying the relationship between each application. Ex. 1014, 59; Ex. 2005, 17; Ex. 2006, 136; Ex. 2007, 263; Ex. 2008, 781; Ex. 2009, 164; Ex. 2011, 2. The '349 patent also maintains continuity of inventorship, Ex. 1014, 2; Ex. 2005, 21; Ex. 2006, 76; Ex. 2007, 206; Ex. 2008, 195; Ex. 2009, 1450; Ex. 2010, 2; Ex. 2011, 1, and continuity of disclosed subject matter, as does each of its predecessor

³ Petitioner addresses U.S. Provisional Applications Nos. 61/441,520 and 61/441,527, which also provide written description for the challenged claims.

Patent Owner focuses here on the '559 application because Wilson is not prior art if the '349 patent has priority to the '559 application.

applications, Ex. 1014, 10-56; Ex. 2005, 29-75; Ex. 2006, 84-130; Ex. 2007, 214-260; Ex. 2008, 232-278; Ex. 2009, 247-293; Ex. 2011, 1-49. Thus, the '349 patent properly claims the benefit of each earlier application in its priority chain and there is no break in priority. Indeed, the Examiner considered the effective filing date of the challenged claims when deciding to examine them “under the pre-AIA first to invent provisions,” based on priority dating to before the AIA implementation date. Ex. 1014, 74; *see infra* Section VII.A.1.

Petitioner’s sole argument is that the common specification fails to provide written description for the challenged claims. But Petitioner has not established a lack of written description. The '559 application discloses the claimed categories of excipients, with specific formulations, representative examples of excipients for each category, and purity levels as claimed. Together, these disclosures provide more than adequate written description for the challenged claims.

1. The '559 Application Provides Written Description For The Challenged Claims

The standard for written description is “whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Written description is an “objective inquiry into the four corners of the

specification from the perspective of a person of ordinary skill” where “the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.” *Id.* The same requirement applies to priority applications, because “a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application.” *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008).

Petitioner fundamentally misconstrues the standard for written description. Written description does not require the disclosure of every possible combination in a pharmaceutical composition. Support for a genus requires “the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350. Even a single species can be representative of a genus. *In re Herschler*, 591 F.2d 693, 701 (C.C.P.A. 1979) (disclosure of single species was sufficient where numerous species were known to skilled artisans). In particular, the number of representative species required to support claimed genus terms is lower where “the claim terms at issue ... are not new or unknown ... materials that ordinarily skilled artisans would easily miscomprehend.” *Amgen Inc. v. Hoechst Marion Roussel*,

Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). In the context of pharmaceutical compositions, there is no requirement to disclose *every* formulation that satisfies the claim. *See In re Entresto (Sacubitril/Valsartan)*, 125 F.4th 1090, 1098 (Fed. Cir. 2025) (finding written description for a pharmaceutical composition where the “invention is plainly described throughout the specification,” including with “[r]epresentative studies,” despite later-discovered formulations not specifically described).

The '559 application satisfies the written description requirement by demonstrating possession of the invention claimed in the '349 patent. The '559 application discloses the inventive cabozantinib (L)-malate API in a pure pharmaceutical composition formulated with well-known excipient categories described in the specification. Specifically, 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.

First, the '559 application includes *ipsis verbis* disclosure of the claimed excipient categories together with a purity level within the claimed range. Specifically, the '559 application discloses the exact same excipient categories as recited in the challenged claims, describing “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***” with a purity level within the claimed range. Ex. 1017, [00127]⁴; *see also id.*, [00104] (same excipients without purity disclosure). That disclosure provides express support for the excipient limitations of the challenged claims in the context of the purity limitation.

In general, claims are supported where they are no broader than the written description. *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 731 (Fed. Cir. 2014) (“In this case, the claim is no broader in scope than the written description.... We have not required more for an adequate written description that matches claim scope.”). The express disclosure of excipient categories in the '559 application is commensurate with the challenged claims, and the '559 application teaches purity within the claimed range.

⁴ Hereinafter, all emphasis is added unless otherwise noted.

Second, the '559 application discloses how to make the claimed formulations, including by teaching how to make the pure API and how to formulate it into tablets or capsules. The '559 application discloses five specific tablet or capsule compositions of Compound IB with representative examples of the claimed excipient types. Ex. 1017, [0022]-[0026]. The specific excipients disclosed are widely used examples for each claimed category, as Petitioner acknowledges. Pet. 37-43 (discussing microcrystalline cellulose as a filler, croscarmellose sodium as a disintegrant, colloidal silicon dioxide as a glidant, and magnesium stearate and stearic acid as lubricants). The '559 application also discloses these formulations with levels of 6,7-dimethoxy-quinoline-4-ol below 200 ppm and as low as 2.5 ppm. Ex. 1017, [00120]-[00126].

Third, the '559 application reports the results of representative stability studies for two capsule formulations with excipients from each claimed category, *see* Ex. 1017, [00162]; Tables 7A, 7B, 8A, 8B, demonstrating “formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.” Ex. 1017, [00163]. Indeed, for the majority of time points, the studies reported single digit ppm purity levels. As Petitioner argues, a POSA would have understood each excipient in those two different capsule formulations is a representative example of the excipient category. *See* Pet. 37-43.

Fourth, the '559 application explains, “[v]arious carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington.” Ex. 1017, [0096]; *see also id.*, [00164] (“All references cited herein are incorporated by reference in their entirety.”). Remington demonstrates that, for each excipient category, the “genus is well understood in the art and not itself the invention but ... instead a component of the claim.”

Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co., 276 F. Supp. 3d 629, 648 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018). By citing and incorporating by reference this well-known treatise, the '559 application points a POSA to exactly the kind of “background knowledge [that] may provide the necessary support for the claim” in such circumstances. *Id.*; *see also Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (explaining that “a patentee may rely on information that is ‘well-known in the art’ for purposes of meeting the written description requirement,” as long as that background knowledge is consistent with the “four corners of the specification”); Ex. 2003, 748:7-17 (Dr. Myerson testifying that formulating a pharmaceutical composition with excipients within the claimed categories was well within the level of skill in the art, based in part on “examples in the patent that inform a

POSA”); Ex. 2002, 394:21-395:2 (Dr. Maureen Donovan testifying that “these excipients are well known” and that “changing one of those excipients to something else in the category for whatever desired purpose, it would be possible”).

* * *

Taken together, a POSA would have understood the disclosures of the ’559 application—including five formulations described as meeting the requisite purity levels and data for two of those formulations—provide written description for the challenged claims. The number of representative species needed to support a claim depends on the subject matter. For example, in *Amgen* the Federal Circuit affirmed that various claims—including one for “[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin [EPO] and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said [EPO] is purified from mammalian cells grown in culture”—had adequate support in the patent specification. 314 F.3d at 1323, 1330-34. Specifically, the court affirmed that “claims covering EPO made using the genus vertebrate or mammalian cells” were adequately supported by “the specification’s description of producing the claimed EPO in two species of vertebrate or mammalian cells.” *Id.* at 1332. The court relied on expert testimony “that those of ordinary skill could ‘easily’ figure out [the] differences in methodology” in adapting the disclosed examples for any

vertebrate or mammalian cell. *Id.* at 1331. The court explained that the representative examples were sufficient, in part, because “the claim terms at issue ... are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.” *Id.* at 1332; *see also Erfindergemeinschaft UroPep*, 276 F. Supp. 3d at 647.

Here, too, the representative examples of excipients and related stability studies support the claimed excipient classes, including because those classes are “not new or unknown” such that a POSA “would easily miscomprehend” them, and a POSA “could ‘easily’ figure out [the] differences in methodology” in formulating other compositions similar to the representative examples disclosed. *Amgen*, 314 F.3d at 1332, 1331. The ’559 application further cites Remington as describing background knowledge for formulating other compositions based on the teachings of the application, including knowledge about excipient categories that the *Amgen* court never questioned a POSA would have had decades earlier.

While the ’559 application describes “known techniques” for adapting the pharmaceutical formulations disclosed, both the importance of minimizing the concentration of 6,7-dimethoxy-quinoline-4-ol, Ex. 1017, [00119], and the synthesis of highly pure cabozantinib (L)-malate allowing that to be achieved, *id.*, [0086]-[0095], were unknown. The novel formulation described in the ’559 application and claimed in the ’349 patent was possible because of Exelixis’

discovery that 6,7-dimethoxy-quinoline-4-ol formed as a degradant at high levels in prior methods of manufacturing cabozantinib (L)-malate and the discovery that this degradant is genotoxic. Significant, non-routine effort went into the identification, quantification, and process control—ultimately resulting in the claimed formulation. *See supra* Section II.B. The significance of the novel synthesis and resulting pharmaceutical formulations was recognized by the Examiner, Ex. 1014, 93-94, and the district court in finding the claims non-obvious. Ex. 1026, 46, 51-53, 67; *see supra* Section II.C. Ground I never addresses the importance of the novel synthesis disclosed in the '559 application to the achievement of the claimed purity in the final pharmaceutical compositions, even though it is a central issue in Petitioner's argument for Ground II. While a POSA would not have expected the synthesis to guarantee a pure final composition, *see infra* Section V.B.1.b, that artisan would have recognized 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. *See supra* Section II.B; Ex. 2002, 605:7-608:10, 696:6-698:7.

2. Petitioner Fails To Consider The Disclosure Of The '559 Application As A Whole

“As the ‘hallmark’ of written description, the disclosure must be considered as a whole, as the person of ordinary skill in the art would read it, to determine if it *reasonably* conveys possession.” *Allergan USA, Inc. v. MSN Labs. Private Ltd.*, 111 F.4th 1358, 1375 (Fed. Cir. 2024) (quoting *Ariad*, 598 F.3d at 1351) (emphasis in original). Petitioner fails to properly consider the whole disclosure of the '559 application, instead attacking individual parts in isolation.

First, Petitioner tries to brush aside the *ipsis verbis* disclosure of the claimed excipient categories. Petitioner cites *Boston Scientific* for the proposition that “*ipsis verbis* disclosure ... is not *per se* sufficient to meet the written description requirement,” Pet. 20 (quoting *Bos. Sci.*, 647 F.3d at 1364), but that case is distinguishable. Unlike the specification in that case, which included “no examples” supporting the claim term, *Bos. Sci.*, 647 F.3d at 1364, the '559 application not only discloses the claimed excipient categories but also includes formulations with representative excipients from each category and stability data for two of those formulations. *See supra* Section V.A.1.

Moreover, while *Boston Scientific* suggests examples *may* be relevant, it explains that “examples are **not** always required to satisfy the written description requirement.” *Bos. Sci.*, 647 F.3d at 1364. The Federal Circuit found the lack of

examples in *Boston Scientific* relevant because of the complexity of the subject matter. *Id.* (finding lack of examples significant “[g]iven the structural complexity of rapamycin”). For excipient limitations relating to “‘known’ methods of preparing pharmaceutical compositions,” as asserted by Petitioner here, Pet. 35, examples are less important for a POSA to understand the inventors possessed the claimed invention.

Petitioner further argues the specification limits the disclosure to its embodiments, pointing to example excipients disclosed in paragraphs [00105]-[00109] and [00128]-[00132]. Pet. 21-22. That is wrong. Paragraphs [00104] and [00127] of the ’559 application expressly state that the embodiment “*relates to* a pharmaceutical composition” with the specific excipient categories (and, for paragraph [00127], within the claimed purity). Ex. 1017, [00104], [00127]. Petitioner identifies nothing in the ’559 application that limits the disclosed invention to just a preferred embodiment of a formulation with one option for each excipient category. Indeed, as noted above, *see supra* Section V.A.1, the ’559 application discloses other formulations that support the challenged claims beyond the embodiment Petitioner alleges is limiting. And even that allegedly limiting embodiment lists *two* different options for the disintegrant. *Id.*, [00129] (“In this embodiment, the disintegrant comprises croscarmellose sodium.”), [00130] (“In

this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.”); *see also id.*, [00106], [00107].

Having attempted to read the *ipsis verbis* disclosure of the excipient categories out of the ’559 application, Petitioner misleadingly argues the February 8, 2021 preliminary amendment adding the challenged claims “is the first time that Patentee used the phrase ‘one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants’ in an unrestricted manner (i.e., without identifying any specific excipient species).” Pet. 27. But a POSA would have understood, based on their plain language, that paragraphs [00104] and [00127] disclose the categories of excipients, supported by specific examples. *See* Ex. 1017, [00127] (“In another embodiment, the disclosure relates to 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 admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.”).

Second, Petitioner’s argument that the three additional compositions for which no stability data was disclosed “provide no useful information” for the written description inquiry is equally flawed. Pet. 24 n.4. Although the ’559 application does not present testing data on those compositions, it specifically describes them as satisfying the purity limitation. *See* Ex. 1017, [00120] (“In one embodiment, the pharmaceutical composition as defined in any of the previous

embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and[]6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.”); *id.*, [00121]-[00126]. Petitioner ignores these disclosures.

Third, for the two disclosed formulations with reported stability data, Petitioner argues “[n]o information can be extrapolated from this data regarding the selection of any other excipient,” because the excipients in the formulations are “virtually identical.” Pet. 24; *see also* Ex. 1007, ¶111. However, Petitioner ignores that the ratios of excipients in the two formulations are different. *See* Ex. 1017, [00161]. Moreover, Petitioner ignores the ’559 application’s citation to Remington, which teaches a POSA armed with the ’559 application’s disclosure how to extrapolate to other excipient formulations. Ex. 1017, [0096]. Indeed, Petitioner relies on Remington in Ground II for exactly that background knowledge. Pet. 37-43.

Fourth, Petitioner’s response to the Remington citation and disclosure that “[v]arious carriers” and “known techniques” can be used is to call it “a generic laundry list.” Pet. 22. Petitioner’s own reliance on Remington in Ground II contradicts its position that Remington is no more than a “laundry list.” *See, e.g.*, Pet. 37-43.

Petitioner cites *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed Cir. 1996), to argue against Remington as relevant to written description. But *Fujikawa* dealt

with a broad genus of chemical compounds described only in terms of lists of possible chemical moieties for various groups. *Id.* The question there was whether such exhaustive lists provided written description for a species or sub-genus with moieties selected from the lists. *Id.* The situation here is different: The '559 application discloses the claimed categories of excipients, formulations with representative excipients for each category, and references Remington for background knowledge about known techniques to formulate compositions with other excipients. Remington is precisely the kind of “background knowledge” that can provide written description for a claim limitation that is “well understood in the art and not itself the invention but is instead a component of the claim.”

Erfindergemeinschaft UroPep, 276 F. Supp. 3d at 647; *see also* Pet. 35

(“Remington would be the type of reference a POSA would consult to understand ‘known’ methods of preparing pharmaceutical compositions.”).

Reviewing the '559 application *as a whole*, as the law requires, a POSA would have understood it adequately supports the challenged claims.

3. Petitioner’s Inconsistent Positions And Misleading Citations To District Court Testimony Cannot Support Their Written Description Argument

Ground I’s premise is that a POSA would have considered formulating pharmaceutical compositions *unpredictable*—even with the benefit of the '559 application’s teachings. *See* Pet. 14-15. But for Ground II, Petitioner asserts the

opposite—that the categories of excipients and specific examples in the ’559 application were well-known, and employed predictably in pharmaceutical compositions. In Ground II Petitioner relies on a statement in Brown that, “[t]he pharmaceutical compositions of this disclosure may be prepared by methods know[n] in the pharmaceutical formulation art, for example, see Remington’s Pharmaceutical Sciences.” Pet. 32 (emphasis omitted) (quoting Brown, [0082]); *see also* Pet. 5-6 (arguing using “customary excipients” was not novel because “Exelixis admitted that such pharmaceutical compositions could be prepared by ‘methods know[n] in the pharmaceutical formulation art’” (citations omitted)). Petitioner argues “Remington would be the type of reference a POSA would consult to understand ‘known’ methods of preparing pharmaceutical compositions.” Pet. 35; *see also id.*, 6-8, 37-44.

Petitioner’s declarant, Dr. Buckton, avoids offering any opinion on the “complexity and predictability of the relevant technology,” which impacts the “level of detail required to satisfy the written description requirement.” *Ariad Pharms.*, 598 F.3d at 1351; *see also id.* (adequacy of written description depends on “the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue” (alteration in original)). Instead of presenting his own view of the scientific facts, Dr. Buckton presents a conclusory opinion based on arguing in the

alternative. *See* Ex. 1007, ¶88 (“[I]t is either the situation that Exelixis is correct about the unpredictable nature of each formulation that is attempted, and if so, there is no written description for claims 1-3 of the ’349 patent given their breadth and the unpredictability of formulation. Or Exelixis is incorrect, in which case the claims of the ’349 patent are obvious over the prior art.”); *id.* ¶163 (similar). But “[e]xpert testimony that does not disclose the underlying facts ... on which the opinion is based is entitled to little or no weight.” 37 C.F.R. § 42.65(a); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985); *Velandar v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003); *U.S. Well Servs., LLC v. Halliburton Energy Servs., Inc.*, IPR2022-01163, Paper 9 at 15 (P.T.A.B. Dec. 20, 2022) (“Although arguing in the alternative is generally permissible, in this case, both the Petition and Petitioner’s expert fail to explain in adequate detail which, why or how the identified elements of [a prior art reference] ... meet the limitations of the challenged claims.”).

Instead of explaining the scientific facts underlying their theories, 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. Dr. Myerson testified about two key differences between the '349 patent and Brown: (1) the “different synthetic process which was designed to minimize the 1-1 impurity at very low levels,” Ex. 2003, 712:4-5, and (2) the “formulation of cabozantinib (L)-malate which is essentially free of the 1-1 impurity,” Ex. 2003, 712:8-9. Dr. Myerson explained that unpredictability was a problem for formulations of API made by the Brown synthesis, not for formulations disclosed in the '349 patent, because the Brown approach “first of all, would make API with variable amounts of the 1-1 impurity, including cases where the 1-1 impurity would already be greater than 200 PPM,” and Brown “doesn’t describe any information on excipient compatibility or any other thing that would allow you to formulate into a drug product that was essentially free [of impurities].” Ex. 2003, 739:3-9.⁵ Dr. Myerson explained the inventors of the '349 patent determined that “any mixture of the API [i.e.,

⁵ The district court found the Exelixis batches addressed at trial, which were not in the prior art, did not exactly follow the Brown experimental process. Ex. 1026, 46 (¶7).

cabozantinib (L)-malate] and excipients generally resulted in an increase in the amount of 1-1 impurity,” which “tells you [] you want to start with a very low level of the 1-1 impurity to ensure that the formulated drug product remains *essentially free*, both when manufactured and on the shelf.” Ex. 2002, 696:6-697:13; *id.* at 702:8-13 (“[I]t’s clear that a key feature of the invention was the ... ability to manufacture API, as described in the ’349 process, that was very, very low in the 1-1 impurity. And, thus, can be formulated into a drug product that could be reliably manufactured and be essentially free of the 1-1 impurity.”).

Despite Dr. Myerson’s clear testimony, Petitioner largely ignores this first key difference to misleadingly imply Dr. Myerson testified the formulations described in the ’559 application fail to support the claimed excipient categories. *See* Pet. 14-15 n.2; Ex. 1007, ¶87. Petitioner’s implausible reading is contradicted by Dr. Myerson’s testimony as a whole. For example, Petitioner alleges that “Exelixis expert admit[ed] that none of these [physiochemical] properties were known in the prior art” and thus a POSA could not “formulate cabozantinib (l)-malate into a drug product that was ‘essentially free’ of the claimed impurity.” Pet. 14 n.2. But Petitioner omits that Dr. Myerson’s testimony was in response to the question, “Without knowing about these properties and *without the benefit of the teaching of the ’349 patent*, could a person of skill have predicted how cabozantinib (L)-malate or levels of the 1-1 impurity would be affected by

formulation?” Dr. Myerson answered no to that question, in the context of his extensive testimony about the benefit the ’349 patent’s disclosure of the novel synthetic process and acceptable pharmaceutical formulations. Ex. 2003, 739:3-740:5. This teaching is included identically in the ’559 application.

The importance of the whole disclosure of the ’349 patent (and thus the ’559 application) is reinforced by other trial testimony Petitioner fails to mention. For example, Dr. Khalid Shah, a co-inventor of the ’349 patent, testified that based on the results from an excipient compatibility study of cabozantinib (L)-malate made via the ’349 patent process, “with most of the excipient combinations we saw an increase in the 1-1 [impurity]. But I’ll point out importantly the starting point ... for the 1-1 was low, ... which was something that we found to be extremely important, given that most of these excipients could give rise to the 1-1.” Ex. 2002, 606:22-607:25. Dr. Shah further testified that the “only way” that a “pharmaceutical composition [of cabozantinib (L)-malate] can be achieved and be essentially free of the 1-1 impurity” would be by “having the lowest levels of the 1-1 impurity possible in the active ingredients. Hence, the commercial process B-2,” which is the process disclosed in the ’349 patent. *See id.*, 649:14-24.

Petitioner hangs its written description theory on misleading snippets of testimony from Exelixis’ witnesses, but none of those witnesses actually testified about written description for the challenged claims. Moreover, trial testimony

Petitioner fails to acknowledge—including from some of the same witnesses—contradicts the conclusions Petitioner urges the Board to draw.

Petitioner failed to demonstrate a reasonable likelihood of prevailing on Ground I.

B. Ground II: Petitioner Has Not Shown Obviousness Over Brown, In View Of Kubo And Remington

Petitioner has not demonstrated a reasonable likelihood of prevailing on obviousness over Brown, Kubo, and Remington. 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 obvious⁶—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. *See* Ex. 1026, 46,

⁶ Claims 2 and 3 specifically require a pharmaceutical composition “essentially free” of 6,7-dimethoxy-quinoline-4-ol. Petitioner never suggests the analysis for claim 1, which covers a pharmaceutical composition “essentially free of process byproducts or contaminants,” should be any different than for claims 2 or 3.

51-53, 67. These deficiencies are not remedied by Kubo or Remington, and Petitioner's attempt to relitigate obviousness fails.

1. Petitioner Fails To Establish Its Combination Of References Discloses Or Suggests All Claim Limitations

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, let alone a pharmaceutical formulation comprising cabozantinib (L)-malate with 200 ppm or less of process byproducts or contaminants. *See* Pet. 30-60. Instead, Petitioner argues it should be excused from identifying where the prior art teaches or suggests the purity limitation because the requisite purity would necessarily have been achieved. Pet. 53-57. Petitioner appears to be implying that the purity limitation would have been inherent in a modified synthesis based on Brown and Kubo. But Petitioner fails to establish that its general combination of Brown and Kubo (with or without Remington) affords a pharmaceutical formulation comprising cabozantinib (L)-malate satisfying the purity limitation in the challenged claims, or that the purity limitation necessarily would be present. Accordingly, Ground II fails.

a. Petitioner Fails To Establish That Its Combination Of References Discloses Or Suggests A Cabozantinib (L)-Malate Composition "Essentially Free Of Process Byproducts Or Contaminants"

The only “process byproduct[] or contaminant[]” addressed by Petitioner is 6,7-dimethoxy-quinoline-4-ol. Pet. 44-60. But Brown, Kubo, and Remington, alone or in combination, do not disclose 6,7-dimethoxy-quinoline-4-ol as an impurity or degradation product, let alone any compositions “essentially free” of 6,7-dimethoxy-quinoline-4-ol.

Petitioner argues “Brown indicates that 6,7-dimethoxy-quinoline-4-ol can remain as a ‘reaction impurity,’” Pet. 45; *see also* Ex. 1027, ¶54, 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 90%wt.% 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 is "essentially free" of 6,7-dimethoxy-quinoline-4-ol. Instead, 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.⁷ See, e.g., Ex. 2002, 669:3-5 (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

⁷ The district court 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. 46.

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 essentially free or less than 200 ppm. Petitioner also fails to acknowledge trial testimony regarding non-prior art information about the levels of 6,7-dimethoxy-quinoline-4-ol actually formed during the Brown process. *See* Pet. 46; Ex. 2002, 693:11-12 (Dr. Myerson testifying that “20[%] of the 1-3 [intermediate] was decomposing to 1-1.”). 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. 52. 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 the decomposition product. Moreover, Petitioner does not even identify the conditions under which Kubo’s approach (*id.*, 12:55-13:1) allegedly would be performed,

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.

Petitioner's general combination of Kubo and Brown does not teach or suggest a cabozantinib (L)-malate composition "essentially free of 6,7-dimethoxy-quinoline-4-ol." Notably, Petitioner wrongly assumes Kubo's "one-step approach is the only difference between Brown's approach to cabozantinib (L)-malate and the '349 patent's approach." Pet. 54. As described in the district court trial testimony, 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. Ex. 1013, ¶54; Ex. 1018, 43; Ex. 2002, 693:14-17, 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 changes 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, Petitioner's proposed combination does nothing to address the additional changes to prevent formation of the 1-1 degradation product in later steps.

Remington does not remedy the deficiencies of Brown and Kubo. Petitioner relies on Remington to disclose excipient categories and individual tablet excipients. Pet. 37-43. But Remington contains nothing that would have informed a POSA about the importance of controlling for 6,7-dimethoxy-quinoline-4-ol during formulation of cabozantinib (L)-malate. On the contrary, it was unknown in the prior art that cabozantinib (L)-malate can react with excipients to form degradation products during the formulation process. Ex. 2002, 661:1-664:6, 696:23-697:21. As such, the addition of Remington to Brown and Kubo would not have taught or suggested a cabozantinib (L)-malate composition "essentially free of 6,7-dimethoxy-quinoline-4-ol."

Thus, Petitioner has not established that its combination discloses or suggests a cabozantinib (L)-malate composition "essentially free of process byproducts or contaminants." The only way Petitioner could supply the missing claim limitation is through inherency. But as discussed below, Petitioner's

arguments implying that the purity limitation would have been inherent from the combination of Brown, Kubo, and Remington fail to meet the high standard required to show inherency.

b. Petitioner Fails To Establish Inherency of The Purity Limitation

Petitioner implies that the purity limitation might have been inherent, arguing the requisite purity “could be” achieved using “known techniques” in a modified synthesis based on Brown and Kubo. Pet. 55-56. But even assuming Petitioner had adequately argued motivation to combine Brown and Kubo divorced from motivation to improve purity (which it has not, *see infra* Section V.B.2), 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. *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 art.”). Indeed, Petitioner never identifies any

conditions under which Kubo’s approach allegedly would be performed—this is insufficient to show inherency of the purity limitation.

Petitioner asserts a Brown-Kubo process “must have necessarily afforded cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol” because Kubo’s “one-step approach is the only difference between Brown’s approach to cabozantinib (L)-malate and the ’349 patent’s approach.” Pet. 53-54. But as discussed above, the synthesis of the ’349 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 1-1 impurity formed. *See supra* Section V.B.1.a. Indeed, even Petitioner’s declarant acknowledges an additional change that would have been required to achieve the synthesis in the ’349 patent. Ex. 1027, ¶50 (observing that “the solvent used in the final crystallization step” is different, which a POSA allegedly “would consider only a minor difference achieved through routine optimization.”). This concession demonstrates the fundamental inadequacy of Petitioner’s inherency argument. *Par Pharm.*, 773 F.3d at 1195-96.

While Petitioner cites cases for the proposition that a claimed invention might have been obvious if it did nothing more than recite an inherent property of an otherwise obvious combination of prior art elements, Pet. 55-56, Petitioner never actually argues the purity limitation would have been inherent in a proposed

Brown-Kubo synthesis with subsequent formulation steps. Instead, Petitioner cites district court testimony from Exelixis' expert, Dr. Myerson, and asserts Exelixis "cannot now contend" the purity limitation would not have been obvious based on the proposed Brown-Kubo combination⁸ or that a pure composition "could [not] be formulated" from the resulting API. Pet. 56. 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 the purity limitation in a formulation.⁹ See Ex. 2003, 773:7-24. He also did not testify that API purity alone could guarantee purity of a pharmaceutical composition. See Ex. 2003, 712:22-713:2 (Myerson) ("[T]he process of blending with excipients and

⁸ Kubo was not part of the district court trial.

⁹ In addition to Petitioner's failure to equate its Brown-Kubo combination with a '349 patent process, *supra* Section V.B.1.a, Petitioner mistakenly relies on enablement to show inherency. See Pet. 55 ("To the extent that the '349 patent *enables* the production of such material, 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.").

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, but end up with a drug product that's not essentially free due to the additional formation of the 1-1.”). Indeed, Drs. Myerson and MacMillan testified at length that the disclosures in the '349 patent—the new synthetic pathway involving multiple changes from Brown, a new recognition of the importance of controlling for 6,7-dimethoxy-quinoline-4-ol, and pharmaceutical compositions including some that had been shown to satisfy the purity limitation—arose from significant, non-obvious improvements.

Petitioner's oblique implication that the disclosures of *the '349 patent and Dr. Myerson's testimony* might demonstrate inherency¹⁰ is divorced from any specific teaching of the prior art and insufficient to meet the high standard for inherency.

Petitioner's inherency argument is further undermined by its own arguments about additional changes that would have been needed to satisfy the claimed purity limitation in the final pharmaceutical formulation. Even with a pure API, Petitioner argues a POSA still would have had to identify the 6,7-dimethoxy-

¹⁰ Petitioner acknowledges Exelixis' experts' testimony that API essentially free of impurities does not necessarily provide a formulation essentially free of impurities in Ground I, *see* Pet. 14 n.2, but ignores it in Ground II.

quinoline-4-ol impurity and control for it in formulating the final pharmaceutical composition. Pet. 57-59. Even if “preparing the dosage form requires nothing more than ‘known techniques,’” Pet. 56, Petitioner does not argue that *any* formulation would have guaranteed the requisite purity level. Indeed, for Ground I Petitioner specifically argues that “[g]iven the unknown interactions, and impurity-producing impacts” of potential excipient combinations, the disclosure of the ’349 patent (including the improved synthesis and examples of substantially pure compositions) would not necessarily or naturally have yielded a pure pharmaceutical composition. Pet. 15. In other words, Petitioner does not argue—let alone establish—that a pure pharmaceutical composition necessarily would have resulted from adopting a proposed modified Brown-Kubo synthesis and formulating the resulting API. Accordingly, Petitioner fails to satisfy the “high standard” required to show inherency. *Par Pharm.*, 773 F.3d at 1195.¹¹

2. Petitioner Fails to Establish a Motivation to Combine

a. Petitioner Fails To Demonstrate Motivation To Modify Brown With Kubo To Achieve The Claimed Purity

¹¹ Petitioner does not rely on Remington for its implied inherency argument. Pet. 44-59. Even if it had, Remington describes known formulation techniques, Pet. 55-56, but does not suggest the requisite purity necessarily would have been achieved in a formulation of API prepared by a Brown-Kubo process.

Petitioner fails to allege (let alone establish) 6,7-dimethoxy-quinoline-4-ol was known before the priority date of the '349 patent as an important genotoxic impurity to control. This is fatal to Petitioner's motivation theory, because, unlike inherency, "[o]bviousness cannot be predicated on what is unknown." *Par Pharm.*, 773 F.3d at 1195 (quoting *In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977)).

According to Petitioner's theory, **first**, a POSA would have modified Brown for efficiency reasons, **not** to control impurities. Pet. 50. **Second**, a POSA would have been motivated by generic regulatory guidance to look for impurities, generally, which would have led to discovering 6,7-dimethoxy-quinoline-4-ol as a "potential impurity." Pet. 57. **Third**, "it would have been *prima facie* obvious [at this point] to minimize the amount of 6,7-dimethoxy-quinoline-4-ol to less than 200 ppm per regulatory guidance." Pet. 58. Petitioner's convoluted path through the prior art requires improper hindsight. *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references....'").

Petitioner fails to acknowledge that the district court specifically found a POSA would **not** have been motivated to control for 6,7-dimethoxy-quinoline-4-ol—despite finding that a POSA would have determined it was genotoxic and subject to FDA guidance. *See* Ex. 1026, 45-46, 52-53 (finding that "a POSA would know from the FDA guidance that the 1-1 starting material is genotoxic,"

but “[b]ecause a POSA would not expect that the 1-1 impurity would be present by the end of the Brown process, the POSA would not be motivated to control for it.”).

Petitioner argues a POSA “would have been motivated to test for its presence and limit the amount of this material in the API and the pharmaceutical composition” “[b]ecause 6,7-dimethoxy-quinoline-4-ol is both a starting material and a potential impurity in cabozantinib (L)-malate.” Pet. 57. But Petitioner never argues that a POSA would have known 6,7-dimethoxy-quinoline-4-ol to be an actual impurity in the Brown process.

Petitioner further argues “Kubo also teaches that the one-step approach can simplify product isolation and improve purity.” Pet. 51. But 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.

b. Petitioner Does Not Demonstrate That A POSA Would Have Modified Brown With Kubo For “Efficiency”

Petitioner asserts a motivation to modify Brown’s process with Kubo’s to eliminate a step and “improve[] efficiency.” Pet. 50. 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 takes the known Brown process—for 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 time and effort to implement and evaluate. Given that the Brown process is “an optimized version of an earlier-developed” process, Ex. 1026, 45, with no drawbacks 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.”

Petitioner’s generic “efficiency” argument is insufficient.

3. The Petition Fails To Establish A Reasonable Expectation Of Success In Controlling 6,7-Dimethoxy-quinoline-4-ol By Modifying Brown With Kubo

For the reasons discussed above in Section V.B.2, a POSA would not have been motivated to modify Brown with the one-step sequence of Kubo. But even if one were to accept Petitioner's premise that such motivation exists, Petitioner's conclusory arguments fail to establish a reasonable expectation of success that such a modified synthesis would have led to a cabozantinib (L)-malate formulation with the claimed purity.

First, Petitioner assumes purported benefits of modifying Brown with Kubo, e.g., "efficiency" and potential improvements in impurity profile, while ignoring potential drawbacks and uncertainties a POSA would have to confront, e.g., changing a known and optimized working synthesis; selecting reaction conditions for the general disclosure in Kubo; using a stronger base that could worsen impurity profile; unknown impact of Kubo's reactions on overall yield and time involved for the modified synthesis. For example, Petitioner argues a POSA would have expected lower amounts of 6,7-dimethoxy-quinoline-4-ol following Kubo's sequence because of "the difference in hydrolytic stability" between the 4-(aminophenoxy)quinoline and the 4-(nitrophenoxy)quinoline intermediates. Pet. 53. Petitioner's declarant states the difference in hydrolytic stability depends on the leaving group ability of 4-nitrophenolate and 4-aminophenolate, which is

“directly correlated with the relative acidities of their respective conjugate acids,” i.e., 4-nitrophenol and 4-aminophenol, where 4-nitrophenol is more acidic. *Id.*; Ex. 1027, ¶78; Ex. 1032, 820. But Petitioner ignores that this difference in relative acidities means a stronger base would be required to achieve Kubo’s one-step sequence with 4-aminophenol (as compared to Brown’s reaction with 4-nitrophenol). Under Petitioner’s own theory of degradation due to hydrolytic instability, a POSA would have been concerned about the potential detrimental impact of using a stronger base—such as more hydrolytic degradation of the reactants and intermediates and an increased level of impurities—which undermines Petitioner’s argument that a POSA would have expected “even lower” amounts of 1-1 from Petitioner’s modified Brown-Kubo synthesis.

Second, as discussed above in Section V.B.2.b, Petitioner does not even identify conditions under which the Brown process modified with Kubo’s one-step sequence purportedly would be performed, completely ignoring the fact that it took Exelixis eight years making significant process changes to develop improved conditions for the synthesis exemplified in the ’349 patent. This is a glaring failure of proof by Petitioner. Petitioner asserts that its general modification of Brown with Kubo “must have necessarily afforded cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol” because the modification with Kubo is “the only difference between Brown’s approach to cabozantinib (L)-

malate and the '349 patent's approach." Pet. 53-54. But the district court record demonstrates that the '349 patent synthesis resulted from numerous "significant" changes made to address various steps during which 6,7-dimethoxy-quinoline-4-ol formed. *See supra* Section V.B.1.b. Even Petitioner's declarant acknowledges that at least one additional change would have been required to achieve the synthesis in the '349 patent. *See* Ex. 1027, ¶50. Petitioner fails to meet its burden of demonstrating a reasonable expectation of success given the experimentation and refinements needed to ensure an API essentially free of impurities.

Third, Petitioner's mischaracterization of the district court record to argue that a POSA would have reasonably expected success in formulating API from a modified Brown-Kubo process into a pharmaceutical composition with the claimed purity also fails. As Dr. Myerson testified in district court, "the 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 [of degradants], but end up with a drug product that's not essentially free due to the additional formation of the 1-1." Ex. 2003, 712:22-713:2. Petitioner itself argues in Ground I that formulating a pharmaceutical composition essentially free of 6,7-dimethoxy-quinoline-4-ol—even with the benefit of the teachings of the '349 patent, i.e., an API with exceptionally low levels of the impurity and specific

formulations with exceptionally low levels—would have required more than routine experimentation and optimization. *See supra* Section V.A.

Petitioner tries to remedy this deficiency in its argument by taking an isolated finding from the district court out of context and twisting its meaning. Specifically, Petitioner cites the district court’s finding that “[i]t was not unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity” and that “[a] POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity.” Pet. 55-56; Ex. 1026, 47 (¶17). But Petitioner omits the remainder of the district court’s finding about the formulations Exelixis was able to make with the API from *the process disclosed in the ’349 patent*, that “[t]he API Exelixis used had very low levels of the 1-1 impurity.” Ex. 1026, 47 (¶17). As the ’349 patent inventor Dr. Shah testified, “very low levels” meant 2-12 ppm of 6,7-dimethoxy-quinoline-4-ol. Ex. 2002, 605:7-18 (“And Exelixis found that the levels of 1-1 were very low. They were in the range of, you know, less than 2 PPM to 12 PPM. So we felt -- Exelixis felt that this was a process by which we were producing the lowest levels of the 1-1 impurity that we possibly could.”).

Petitioner never establishes that its Brown-Kubo synthesis would have produced cabozantinib (L)-malate having the “very low” levels of 1-1 that the court

found “could” be formulated into a composition essentially free of 1-1. Thus, the district court’s findings do not support Petitioner’s theory.

* * *

Even assuming a POSA would have been motivated to modify Brown with the one-step sequence of Kubo, as Petitioner contends, Petitioner fails to establish reasonable expectation of success in arriving at the claimed formulation based on its proposed combination.

VI. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

Objective indicia of nonobviousness are not just “cumulative or confirmatory ... but constitute[] independent evidence of nonobviousness.” *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). 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. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(D)

The Petition presents art and arguments substantially the same as those already considered by the Office and the district court, and therefore runs counter to the judicial economy § 325(d) is intended to promote. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH* provides for considering (1) “whether the same or substantially the same art [or arguments] previously was presented to

the Office”; and (2) “if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.” IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential). Both prongs favor denial here.

A. *Advanced Bionics* Prong 1

In evaluating whether the same or substantially the same art or arguments were previously presented to the Office, the Board considers the following *Becton Dickinson* (“*BD*”) factors: (a) similarities and material differences between the Petition’s art and the art involved during examination; (b) the cumulative nature of the Petition’s art and the art evaluated during examination; and (d) the extent of overlap between arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art. *See id.* at 9-10; *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 11-12 (P.T.A.B. Sept. 12, 2018) (precedential) (quoting *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (informative)).

BD factors (a), (b), and (d) favor denial.

1. Ground I

Petitioner argues *Advanced Bionics* does not apply to Ground I because “[t]he effective filing date of the challenged claims was not considered during

examination,” and therefore “the Office was not presented the same art or the same arguments.” Pet. 66.

Petitioner is incorrect: The Office was presented with Wilson, an ancestor of the challenged patent. *See* Ex. 1001, (60) (“Related U.S. Application Data” showing applications connecting Wilson to the challenged patent). The challenged patent and Wilson share the same specification, meaning the substance of Wilson was before the Office throughout examination.

Additionally, Applicant consistently called out Wilson to the Office in listings of “other applications related to c-Met inhibitors,” Ex. 1014, 64, 85, 116, and on an Information Disclosure Statement (“IDS”) considered by the Examiner, *see, e.g.*, Ex. 2012, 17 (listing Wilson with notation, “ALL REFERENCES CONSIDERED”). The Examiner listed Wilson on a Notice of References Cited. Ex. 2012, 10.

The Office also rejected the challenged claims for non-statutory double patenting over Wilson (which was overcome by terminal disclaimer). Ex. 1014, 76, 114. In this rejection, the Examiner alleged, as does Petitioner, that Wilson discloses cabozantinib (L)-malate and its pharmaceutical compositions. *Id.*, 76-77; Pet. 28. Accordingly, Wilson was presented to and considered by the Office.

Petitioner is also incorrect that the effective filing date of the challenged claims was not considered during examination. The Examiner considered it when

deciding to examine the claims “under the pre-AIA first to invent provisions.” Ex. 1014, 74. Because the application that became the challenged patent was filed after the implementation date of the AIA, the Examiner necessarily determined that the application was entitled to an earlier effective filing date.

2. Ground II

Ground II alleges obviousness over Brown in view of Kubo and Remington. Pet. 9. Brown was asserted by the Examiner as an obviousness reference. *See* Ex. 1014, 93-94 (Office Action rejecting claims as obvious over, *inter alia*, Brown). Furthermore, the Office raised substantially the same arguments vis-à-vis Brown as the Petition. *See id.* (alleging Brown teaches cabozantinib (L)-malate, substantially pure, in combination with pharmaceutically acceptable excipients, such as fillers, glidants, disintegrants, and lubricants).

Petitioner argues the Office failed to consider the combination of Brown with Kubo. *See* Pet. 66. However, during prosecution of the application that became U.S. Patent 10,123,999 (“’999 Patent”)—an ancestor of the challenged patent—the Office rejected the claims as obvious over Brown in view of Kubo. Ex. 2008, 760-763. The Office asserted that while Brown does not use the same one-step procedure to make the amine-substituted intermediate as the challenged patent, Kubo allegedly does. *Id.*

The Office argued (1) a POSA would have been motivated to modify Brown with the one-step procedure in Kubo “by the desire in the art to reduce unnecessary steps”; and (2) Kubo’s “compounds are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties.” Ex. 2008, 760-763; *see also* Pet. 33-34, 45-51. The Office thus combined the same disclosure in Brown and Kubo as Petitioner, with the same argument for motivation to combine, which Applicant overcame. While the claims prosecuted in the ’999 Patent were process claims, the Office’s consideration of Kubo is applicable to the challenged claims, because “[t]he factors set forth in *Becton, Dickinson* should be read broadly ... to apply to any situation in which a petition relies on the same or substantially the same art or arguments previously presented to the Office ... during *any* proceeding.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 10 (emphasis in original).

Additionally, Kubo was cited in an IDS considered by the Office during examination of the challenged patent. *See* Ex. 2012, 17.

Petitioner further argues the Office did not consider Remington and its disclosure of excipients for use in tablet compositions. *See* Pet. 66-67. Petitioner ignores key parts of the record. **First**, Remington is cited and incorporated by reference in the specification. Ex. 1001, 20:38-49.

Second, during examination of the challenged patent, the Office rejected claims as obvious over a Brown family member in view of references substantially similar to Remington: (1) Li *et al.*, Lubricants in Pharmaceutical Solid Dosage Form; (2) Pingali *et al.*, Mixing Order of Glidant and Lubricant—Influence on Powder and Tablet Properties; and (3) Overview of Pharmaceutical Excipients Used in Tablets and Capsules. Ex. 1014, 93-94; *see also* Ex. 2012, 246 (Examiner’s Notice of References Cited). Like Remington, these references provide general overviews of excipients and were relied on by the Office the same way Petitioner relies on Remington—to assert that the claimed excipients were known and a POSA would have known how to use them. *Compare* Ex. 1014, 94-96, *with* Pet. 35-44, 66-67.

B. *Advanced Bionics* Prong 2

In evaluating whether Petitioner has demonstrated the Office erred in a manner material to patentability, the Board considers *BD* factors (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 10-11. These considerations favor denial.

1. *BD* Factor (c)

a. Ground I

As discussed above in Section VII.A.1, the Office expressly considered Wilson during examination.

While the Office did not discuss Wilson in the context of an effective filing date or written description challenge, *BD* factor (c) does not require that “each and every argument set forth in the petition must have been previously presented.”

Ziegmann v. Stephens, IPR2015-01860, Paper 13 at 19 (P.T.A.B. Sept. 6, 2017).

As discussed above, the Office did consider the effective filing date of the challenged patent through determining its AIA status. *See supra* Section VII.A.1.

b. Ground II

As discussed above, the Office extensively considered Brown, individually and in view of Kubo, during examination of the challenged patent and its ancestors. *See supra* Section VII.A.2. Claims were rejected over Brown in view of Kubo in an ancestor application. Because those claims recited the synthetic process, Applicant overcame the rejection through amendments emphasizing process differences with Kubo. *See Ex. 2008, 1271* (Response to Non-Final Rejection, Apr. 17, 2018). Nevertheless, as discussed *supra* in Section VII.A.2, the Office’s consideration of Brown in view of Kubo applies to the challenged

claims given the similarity to the Petition of the asserted disclosure and the Examiner's arguments on motivation to combine.

Remington was considered by the Office because it is cited and incorporated by reference in the specification, in the same manner asserted by Petitioner. *See supra* Section VII.A.2.

Further, the Examiner rejected the claims in view of analogous general reference works on common excipients. *See supra* Section VII.A.2.

2. BD Factor (e)

“[W]hen a prior art reference presented in a petition was already considered substantively [during examination], the petitioner has the initial burden to identify such errors made by the examiner with respect to that ... reference.” *Ziegmann*, IPR2015-01860, Paper 13 at 10. Material error can include “misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims” or legal error, such as an incorrect claim construction. *Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9, n.9.

a. Ground I

Petitioner merely states that *Advanced Bionics* does not apply because the Office allegedly was not presented the same art or arguments as in Ground I. Pet. 66. Petitioner has not met its burden to identify any Examiner error. And there is none. The Office did not “misapprehend[] or overlook[] specific teachings” of

Wilson. Rather, it dutifully considered Wilson on an IDS, issued a double patenting rejection over Wilson, and considered Wilson's disclosure (common to the challenged patent's family) in determining that the application's effective filing date afforded pre-AIA status. *See supra* Section VII.A.1.

b. Ground II

Petitioner alleges "the Examiner plainly erred by relying solely on a theory of single-reference obviousness while failing to consider the Challenged Claims' recitation of common categories of pharmaceutical excipients." Pet. 66.

Petitioner's position is flawed. **First**, the portion of the file history Petitioner cites, Ex. 1014, 82, does not address obviousness; it is an anticipation rejection. **Second**, the Office did not raise a single-reference obviousness rejection. As discussed above, it raised obviousness combinations. In the ancestor application, the Office rejected the claims over Brown in view of Kubo, asserting the same disclosure and arguments advanced by Petitioner. *See supra* Section VII.A.2. In the challenged patent, the Office rejected the claims over Brown in view of Li, Pignali, and Overview of Pharmaceutical Excipients. Ex. 1014, 93-96. In doing so, it asserted the very disclosure of common excipients that Petitioner claims was not considered. *See supra* Section VII.A.2.

Petitioner further alleges that the Office erred by failing to consider a pharmaceutical treatise like Remington. Pet. 66-67. As discussed above,

Remington was cited and incorporated by reference in the specification, and the Office rejected the claims over substantially similar references generally disclosing excipients for tablet compositions. Here again the Office asserted the very disclosure Petitioner claims was not considered.

3. *BD* Factor (f)

Petitioner did not present any additional evidence for Ground I that warrants reconsideration of Wilson and Petitioner's effective filing date arguments.

For Ground II, Petitioner alleged that "the Examiner did not have the benefit of Exelixis'[] admissions and expert's statements regarding a motivation to formulate cabozantinib (L)-malate with each of the excipient categories recited in the Challenged Claims." Pet. 66. Petitioner suggests that, had it, the Examiner would not have "acquiesced to Exelixis'[] arguments regarding purity or the incorporation of a glidant." *Id.*

As an initial matter, Petitioner mischaracterizes Exelixis' experts' testimony. *See supra* Section V. The district court considered the experts' complete testimony and, like the Office, found challenged claim 3 non-obvious over Brown. *See Ex.*

1026, 46, 51-53, 67. Petitioner has presented no evidence that the Office would have found differently had it considered the full district court record.¹²

Furthermore, prosecution of the '349 patent's progeny demonstrates that having the district court record would not have affected the Office's determination of patentability. Several documents from the trial record were submitted in an IDS, which the Examiner considered, during prosecution of U.S. Patent 12,128,039, a child of the challenged patent. *See* Ex. 2013, 71. The Board can consider the prosecution history of a child application when determining whether to deny institution of a post-grant proceeding against a parent patent. *See Live Nation Ent., Inc., v. Complete Ent. Res. B.V.*, PGR2017-00038, Paper 11 (P.T.A.B. Jan. 16, 2018). In *Live Nation*, the Board denied institution under § 325(d) because the claims of the child were similar to the parent and the petition presented substantially the same arguments and art as the Office considered during prosecution of the child. *See id.* at 8-9, 17-18. Here, the same considerations apply: The challenged claims and the child claims are directed to a cabozantinib (L)-malate composition with a specified amount of 1-1 impurity, and the same art

¹² As discussed above, Petitioner offers no argument why the analysis for claims 1 and 2 should be any different than for claim 3. *See supra* Section I and n.6.

was considered during prosecution of each application. *See* Ex. 2013, 122, 264 (claims), 139-141 (rejection over Brown); 150 (IDS citing Kubo and Wilson).

Among the materials considered in the child application was MSN's Opening Post-Trial Brief on Invalidity. Ex. 2014. The Brief substantially overlaps with Petitioner's Ground II. *Compare id.*, 19, 30-31, *with* Pet. 54, 56; Ex. 2014, 21-22, *with* Pet. 46, 59; Ex. 2014, 26-28, *with* Pet. 57-58.

Despite considering these materials from the district court litigation, the Office allowed the claims over a Brown family member, finding that Brown "does not have the 'less than 100ppm' in the claims or specification." *See* Ex. 2013, 118 (Examiner Interview Summary, Apr. 18, 2024). Accordingly, Petitioner's purported additional evidence does not warrant reconsideration.

All *Advanced Bionics* and *BD* factors support denying institution under § 325(d).

VIII. THE PETITION SHOULD BE DENIED BECAUSE IT REARGUES ISSUES LITIGATED IN DISTRICT COURT

The Board should further exercise its discretion to deny institution because Petitioner merely repackages and reargues substantially the same issues litigated in district court while ignoring the district court's holding of non-obviousness and mischaracterizing the testimony of Exelixis' witnesses. *See supra* Section II.C. Petitioner makes incomplete arguments around inherency, motivation to combine,

and reasonable expectations for success that add no new data to, and cannot rehabilitate, the invalidity arguments that failed in district court. Petitioner relies on the same primary obviousness reference (Brown) considered by the district court but claims its obviousness challenge is different from that rejected by the district court because Petitioner is challenging all claims. Pet. 63. But Petitioner never articulates any reason that claims 1 and 2 should be analyzed any differently than claim 3 (considered by the district court). Pet. 11-30 (addressing “Challenged Claims” together under Ground 1), 60. Accordingly, these additional claims present nothing new for the Board to consider. Furthermore, Petitioner relies heavily on the testimony of Exelixis’ own experts from the district court supporting validity of the ’349 patent to try to support its positions. The district court considered this evidence in its entirety—not just the cherry-picked statements Petitioner misleadingly presents—and ruled for Exelixis. This petition does not reflect new arguments warranting the Board’s consideration; institution would be an inefficient use of Board resources.

The Board has exercised its discretion under both § 314(a) and § 325(d) to deny institution based on an advanced district court case raising similar grounds as a petition. In *Mylan Pharmaceuticals Inc. v. Bayer Intellectual Property GmbH*, the Board denied institution under § 314(a), citing (1) the advanced stage of a co-pending district court case, (2) the significant overlap of prior art between the

petition and the district court case, and (3) the similarity in claim construction and expert testimony in the two proceedings. IPR2018-01143, Paper 13 at 13-14 (P.T.A.B. Dec. 3, 2018). The Board concluded “it would be an inefficient use of Board resources to proceed with this *inter partes* review in parallel with the district court case.” *Id.* at 13 (citing *NHK Spring Co. v. Intrix-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 19-20 (P.T.A.B. Sept. 12, 2018)); *see also Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 6 (P.T.A.B. Mar. 20, 2020) (precedential) (identifying non-exclusive factors the Board has considered to determine “whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding”); *Amazon.com, Inc. v. Vocalife LLC*, IPR2020-00864, Paper 22 at 19 (P.T.A.B. Oct. 28, 2020) (denying institution where the issues between the district court case and the Petition only “partly overlap[ped]” based on “holistic analysis”).

In *Neptune Generics, LLC v. Aventis Pharma S.A.*, the Board considered a parallel district court case—in which the petitioner was not a party—in denying institution under § 325(d). IPR2019-00136, Paper 15 at 35-37 (P.T.A.B. May 6, 2019). There, the petitioner relied on the same art as in the district court case, and the Board had already denied institution of a substantially similar obviousness challenge in a separate petition. *Id.* at 36. The Board explained that “the stage and significant subject-matter overlap of the court proceedings, with a decision from

the Federal Circuit likely to come before the Board would complete the trial proceedings ..., tilt in favor of restraint and discretionary denial of this Petition.”

Id. at 37.

Here, the completed trial based on significantly overlapping subject matter similarly justifies restraint. Petitioner’s attempt to support its arguments with isolated, out-of-context testimony from the district court, while ignoring the decision rendered, does not merit the Board’s limited time and resources. The Board should deny institution.

IX. CONCLUSION

Patent Owner respectfully requests denial of institution.

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

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	File History (Partial) for U.S. Patent Application No. 17/152,394
2006	File History (Partial) for U.S. Patent Application No. 16/706,323
2007	File History (Partial) for U.S. Patent Application No. 16/151,653
2008	File History (Partial) for U.S. Patent Application No. 15/348,716
2009	File History (Partial) for U.S. Patent Application No. 13/984,559
2010	PCT Request for International Application No. PCT/US2012/024591 (Feb. 10, 2012)
2011	International Publication No. WO 2012/109510 A1 (Aug. 16, 2012)
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.)

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response contains 13,858 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/
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CERTIFICATE OF SERVICE

I hereby certify that on March 11, 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
- Exhibits 2001-2014

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

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