

Filed November 18, 2024

On behalf of **AZURITY PHARMACEUTICALS, INC.**

By: Andrew Morrell, Ajay Kayal, Leah Digby
WINDELS MARX LANE & MITTENDORF, LLP
One Giralda Farms
Madison, NJ 07940
Tel.: 973-966-3200 Fax: 976-966-3250
Email: AzurityIPRs@windelsmarx.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.

Petitioner,

v.

EXELIXIS, INC.

Patent Owner.

IPR2025-00210
Patent 11,298,349

**PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT 11,298,349**

TABLE OF CONTENTS

	Page No.
I. INTRODUCTION	1
II. STATE OF THE ART.....	4
A. Cabozantinib and Its Malate Salt	4
B. Orally Administered Tablets and Capsules are Preferred Pharmaceutical Compositions	6
1. Fillers.....	7
2. Disintegrants	7
3. Glidants	8
4. Lubricants.....	8
III. THE CHALLENGED CLAIMS ARE UNPATENTABLE	8
A. Grounds of Challenges	9
B. The Prior Art	9
IV. LEVEL OF ORDINARY SKILL IN THE ART	10
V. CLAIM CONSTRUCTION	10
A. Claim 1 – “essentially free of process byproducts or contaminants”	10
B. Claim 3 – “essentially free of 6,7-dimethoxy-quinoline-4-ol”	11
VI. GROUND 1: ANTICIPATION BY WILSON.....	11
A. Wilson is Prior Art to the Challenged Claims.....	11

TABLE OF CONTENTS
(cont'd)

	Page No.
1. No presumption of an earlier priority date.....	12
2. Exelixis's broad claims make compliance with the written description requirement impossible.....	13
3. The '349 patent's "priority" applications do not convey possession of the breadth of the Challenged Claims	17
a. The '520 provisional does not disclose any compositions	17
b. The '527 provisional omits pertinent limitations	18
c. The '559 application fails to convey possession	20
d. Other generalized disclosures in the '559 application do not provide support for the Challenged Claims.....	22
e. Species in the '559 application do not convey possession of broader claims	23
f. The '716, '653, '323, and '394 applications fail to afford any additional written description support	25
B. The Effective Filing Date of the Challenged Claims Can Only Be February 8, 2021	26
C. Wilson Discloses a Species that Anticipates the Broad Genus Claims of the '349 Patent.....	28

TABLE OF CONTENTS
(cont'd)

	Page No.
VII. GROUND 2: OBVIOUSNESS OVER BROWN IN VIEW OF KUBO AND REMINGTON	30
A. Introduction to Brown	31
B. Introduction to Kubo	33
C. Introduction to Remington	35
D. Brown in view of Kubo and Remington Render the Challenged Claims Obvious.....	36
1. Claim 1	36
a. Preamble	36
b. Compound IB.....	36
c. Fillers	37
d. Disintegrants	38
e. Glidants.....	40
f. Lubricants	41
g. Tablet/Capsule	43
h. Achieving “Essentially Free” Levels of “Process Byproducts and Contaminants” Would Have Been Obvious	44
i. Cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline- 4-ol would have been obvious.....	45

TABLE OF CONTENTS
(cont'd)

	Page No.
ii. A pharmaceutical composition containing 200 ppm or less of 6,7- dimethoxy-quinoline-4-ol would have been obvious.....	55
2. Claim 2.....	60
3. Claim 3.....	60
VIII. SECONDARY CONSIDERATIONS	60
IX. INSTITUTION IS WARRANTED	61
A. The <i>Fintiv</i> Factors do not Favor Denial	61
1. <i>Fintiv</i> Factor 1 Disfavors Denial.....	62
2. <i>Fintiv</i> Factor 2 Disfavors Denial.....	62
3. <i>Fintiv</i> Factors 3 and 4 Disfavor Denial.....	62
4. <i>Fintiv</i> Factor 5 Disfavors Denial.....	64
5. <i>Fintiv</i> Factor 6 Disfavors Denial.....	64
B. The <i>Advanced Bionics</i> Test Does Not Favor Denial.....	65
1. <i>Advanced Bionics</i> does not apply to Ground 1	66
2. <i>Advanced Bionics</i> favors institution for Ground 2	66
X. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(A)(1)	67
A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))	67

TABLE OF CONTENTS
(cont'd)

	Page No.
B. Related Matters (37 C.F.R. §42.8(b)(2)).....	67
C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))	68
D. Service Information (37 C.F.R. §42.8(b)(4))	69
XI. PAYMENT OF FEES.....	69
XII. ADDITIONAL REQUIREMENTS UNDER 37 C.F.R. §42.104.....	69
XIII. CONCLUSION	69

TABLE OF AUTHORITIES

Page No(s).

<i>ACCO Brands Corp. v. Fellowes, Inc.</i> , 813 F.3d 1361 (Fed. Cir. 2016)	49
<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH</i> , IPR2019-01469 (PTAB Feb. 13, 2020)	65
<i>Abbvie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.</i> , 759 F.3d 1285 (Fed. Cir. 2014)	16
<i>Apple, Inc. v. Fintiv, Inc.</i> , IPR2020-00019 (PTAB Mar. 20, 2020)	61
<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010)	13, 16, 23
<i>Atlas Powder Co. v. Ireco Inc.</i> , 190 F.3d 1342 (Fed. Cir. 1999)	28
<i>Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001)	56-57
<i>Bos. Sci. Corp. v. Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011)	20
<i>Commscope Tech. LLC v. Dali Wireless, Inc.</i> , IPR2022-01242 (PTAB Feb. 27, 2023)	64, 65
<i>In re Curtis</i> , 354 F.3d 1347 (Fed. Cir. 2004)	16
<i>Dynamic Drinkware, LLC v. National Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	12, 13
<i>Fiers v. Revel</i> , 984 F.2d 1164 (Fed. Cir. 1993)	16

TABLE OF AUTHORITIES

(cont'd)

Page No(s).

<i>Fujikawa v. Wattanasin</i> , 93 F.3d 1559 (Fed. Cir. 1996)	19, 22
<i>In re Grimme</i> , 274 F.2d 949 (CCPA 1960)	17
<i>Idenix Pharms. LLC v. Gilead Scis. Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019)	16
<i>Juno Therapeutics, Inc. v. Kite Pharma, Inc.</i> , 10 F.4th 1330 (Fed. Cir. 2021)	16-17
<i>King Pharms., Inc. v. Eon Labs, Inc.</i> , 616 F.3d 1267 (Fed. Cir. 2010)	55
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	49
<i>Ex parte Kubin</i> , 2007 Pat. App. LEXIS 13, *9-10, 83 U.S.P.Q.2D (BNA) 1410, 1413-1414 (Bd. Pat. App. & Interferences May 31, 2007)	30-31
<i>LizardTech, Inc. v. Earth Res. Mapping, Inc.</i> , 424 F.3d 1336 (Fed. Cir. 2005)	17
<i>Leapfrog v. Fisher-Price</i> , 485 F.3d 1157 (Fed. Cir. 2007)	61
<i>MEHL/Biophile Int'l Corp. v. Milgraum</i> , 192 F.3d 1362 (Fed. Cir. 1999)	54, 59
<i>Nat. Alternatives Int'l, Inc. v. Iancu</i> , 904 F.3d 1375 (Fed. Cir. 2018)	27
<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.</i> , 868 F.3d 1013 (Fed. Cir. 2017)	10

TABLE OF AUTHORITIES

(cont'd)

Page No(s).

<i>Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.</i> , 923 F.3d 1368 (Fed. Cir. 2019)	14, 20, 21
<i>In re Peterson</i> , 315 F.3d 1325 (Fed. Cir. 2003)	58
<i>In re NTP, Inc.</i> , 654 F.3d 1268 (Fed. Cir. 2011)	12
<i>Persion Pharm. LLC v. Alvogen Malta Operations Ltd.</i> , 945 F.3d 1184 (Fed. Cir. 2019)	56
<i>PowerOasis, Inc. v. T-Mobile USA, Inc.</i> , 522 F.3d 1299 (Fed. Cir. 2008)	12
<i>Regents of the Univ. of Minn. v. Gilead Scis., Inc.</i> , 61 F.4th 1350 (Fed. Cir. 2023)	25
<i>Rsch. Corp. Techs. v. Microsoft Corp.</i> , 627 F.3d 859 (Fed. Cir. 2010)	13
<i>Santarus, Inc. v. Par Pharm., Inc.</i> , 694 F.3d 1344 (Fed. Cir. 2012)	57
<i>Technology v. Videotek</i> , 545 F.3d 1316 (Fed. Cir. 2008)	13
<i>Tronzo v. Biomet, Inc.</i> , 156 F.3d 1154 (Fed. Cir. 1998)	13, 21, 30
<i>Wyers v. Master Lock Co.</i> , 616 F.3d 1231 (Fed. Cir. 2010)	49

TABLE OF AUTHORITIES
(*cont'd*)

Page No(s).

OTHER AUTHORITIES

35 U.S.C. §102.....	3
35 U.S.C. §102(a)	9
35 U.S.C. §102(b)	9
35 U.S.C. §102(a)(1).....	9
35 U.S.C. §103	3
35 U.S.C. §112	12
35 U.S.C. §119(e)(1).....	12
35 U.S.C. §282.....	10
35 U.S.C. §314(a)	61
35 U.S.C. §325(d)	61
37 C.F.R. §42.8	67, 68, 69
37 C.F.R. §42.15(a).....	69
37 C.F.R. §42.100(b)	10
37 C.F.R. §42.104	69
M.P.E.P. §2163	17, 27

EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent 11,298,349 (“the ’349 patent”)
1002	U.S. Patent 9,717,720 (“Wilson”)
1003	WO 2010/083414 (“Brown”)
1004	Remington: The Science and Practice of Pharmacy, 21st Edition (2005) (“Remington”)
1005	CABOMETYX® Product Insert
1006	COMETRIQ® Product Insert
1007	Declaration of Graham Buckton, Ph.D.
1008	U.S. Patent 7,579,473 (“the ’473 patent”)
1009	Mark Gibson, “Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form,” Informa Healthcare USA, Inc. (2009) (“Gibson”)
1010	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 168 (D.Del.)
1011	<i>Exhibit Number Not Used</i>
1012	<i>Exhibit Number Not Used</i>
1013	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 176 (D.Del.)
1014	Prosecution History excerpt for U.S. Application Serial No. 17/170,275
1015	U.S. Provisional Application Serial No. 61/441,520 (“the ’520 provisional”)
1016	U.S. Provisional Application Serial No. 61/441,527 (“the ’527 provisional”)

Exhibit No.	Description
1017	Prosecution History excerpt for U.S. Application Serial No. 13/984,559 (“the ’559 application”)
1018	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 175 (D.Del.)
1019	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 163 (D.Del.)
1020	Prosecution History excerpt for U.S. Application Serial No. 15/348,716 (“the ’716 application”)
1021	Prosecution History excerpt for U.S. Application Serial No. 16/151,653 (“the ’653 application”)
1022	Prosecution History excerpt for U.S. Application Serial No. 16/706,323 (“the ’323 application”)
1023	Prosecution History excerpt for U.S. Application Serial No. 17/152,394 (“the ’394 application”)
1024	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 162 (D.Del.)
1025	Rowe et al., “Handbook of Pharmaceutical Excipients,” 6 th Ed. (2009)
1026	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 186 (D.Del.)
1027	Declaration of William Dichtel, Ph.D.
1028	U.S. Patent 7,169,789 (“Kubo”)
1029	Hoffmann, “Elements of Synthesis Planning,” (2009), 133-144
1030	Newhouse <i>et al.</i> , “The economies of synthesis,” <i>Chem. Soc. Rev.</i> , 38 (2009), 3010-3021 (“Newhouse”)
1031	Burns <i>et al.</i> , “Redox Economy in Organic Synthesis,” <i>Angew. Chem. Int. Ed.</i> , 48 (2009), 2854-2867
1032	Pross <i>et al.</i> , “Theoretical Approach to Substituent Effects. Phenols and Phenoxide Ions,” <i>J. Org. Chem.</i> , 45 (1980), 818-826

Exhibit No.	Description
1033	Furuta <i>et al.</i> , “Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation,” <i>J. Med. Chem.</i> , 49 (2006), 2186-2192.
1034	Aulton, Chapter 31 (“Dosage Form Design and Manufacture”) 3 rd Edition
1035	Felpin <i>et al.</i> , “A Useful, Reliable and Safer Protocol for Hydrogenation and the Hydrogenolysis of O-Benzyl Groups: The In Situ Preparation of an Active Pd0/C Catalyst with Well-Defined Properties,” <i>Chem. Eur. J.</i> , 16 (2010), 12440-12445.
1036	Toxicological Review of Quinoline (2001) by the U.S. Environmental Protection Agency
1037	Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008)
1038	European Medicines Agency, Guideline on the Limits of Genotoxic Impurities (2006)

Azurity Pharmaceuticals, Inc. (“Azurity” or “Petitioner”) requests *inter partes* review (“IPR”) of claims 1-3 (“Challenged Claims”) of U.S. 11,298,349 (“the ’349 patent”) (Ex. 1001) purportedly owned by Exelixis, Inc. (“Exelixis” or “Patentee”). These claims are: (1) anticipated by an earlier family member; and (2) obvious in light of the prior art.

I. INTRODUCTION

The ’349 patent claims a capsule or tablet formulation of a previously known compound, cabozantinib (L)-malate (denoted “Compound IB”), in combination with generic categories of excipients (i.e., fillers, disintegrants, glidants, and lubricants) that is “essentially free of process byproducts or contaminants” (claim 1) or “of 6,7-dimethoxy-quinoline-4-ol” (claims 2 and 3). Ex. 1001 at 34:5-51. The claims do not require any specific excipients that would afford a formulation “essentially free” of the unwanted “process byproducts or contaminants.” Instead, the Challenged Claims encompass millions of permutations of excipients, to be randomly picked from the broadly recited categories, constrained only by the result to be achieved. Such result-defined, broad claims should have never been allowed.

Ground 1: Anticipation

The Challenged Claims are anticipated by a family member – Wilson (Ex. 1002). Wilson issued on August 1, 2017—over three-and-a-half years before the February 8, 2021 filing date of the application that led to the ’349 patent. Wilson

reports a capsule made with cabozantinib (L)-malate (“Compound IB”) that is essentially free of the 6,7-dimethoxy-quinoline-4-ol impurity and formulated with certain specific excipients (that all fall within the broad excipient categories set forth the ’349 patent claims). Anticipation of the Challenged Claims is self-evident upon comparison.

The ’349 patent purports to have priority reaching back to the application that led to Wilson’s issuance. That is not so. There is no written description support for the breadth of the Challenged Claims in these earlier applications. Nothing about their description conveys possession of pharmaceutical compositions that meet a purity requirement utilizing any filler, any disintegrant, any glidant, and any lubricant as later claimed. Rather, the written description is limited to certain, exacting species of excipients from two working examples exhibiting the requisite purity regarding 6,7-dimethoxy-quinoline-4-ol when evaluated using undisclosed methodology. Accordingly, the Challenged Claims are broader than described and that breadth of scope only appeared for the first time in a preliminary amendment submitted on February 8, 2021 that introduced new matter. Thus, the exemplified species of capsule disclosed in Wilson’s examples are prior art to the ’349 patent and anticipate the Challenged Claims.

Ground 2: Obviousness

The claims of the '349 patent would have been obvious over Exelixis's own prior art reference, Brown (Ex. 1003), in view of Kubo (Ex. 1028) and Remington (Ex. 1004).

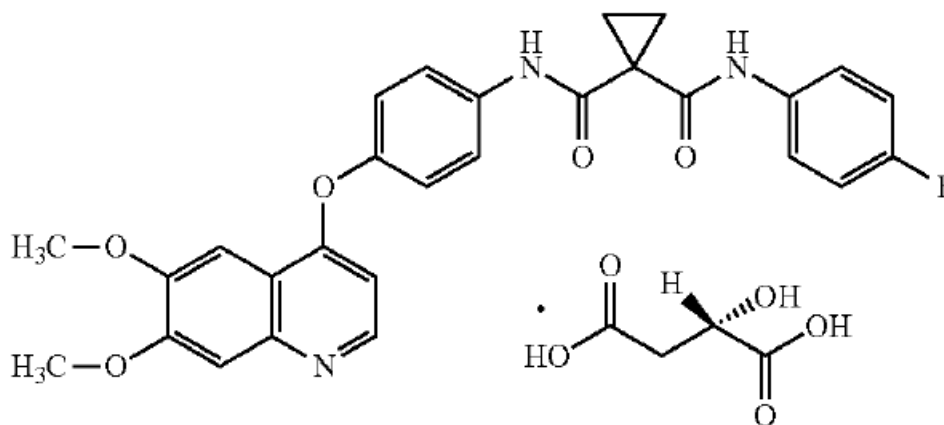
Each limitation of the Challenged Claims was either expressly disclosed in the prior art or was manifestly obvious. Brown disclosed Compound IB and the idea of putting it in an oral dosage form (e.g., a tablet or capsule) using known techniques and common excipients from Remington. Moreover, Brown provided a synthetic route for making Compound IB that afforded "de minimis" levels of 6,7-dimethoxy-quinoline-4-ol using 6,7-dimethoxy-quinoline-4-ol as the starting material. Brown's route to Compound IB only differs from the '349 patent's synthetic route by virtue of an obvious change that Kubo referred to as an "alternative" approach—one that was more efficient and expected to reduce the amount of a potentially genotoxic impurity. Thus, a simple substitution within Brown's synthetic path affords that of the '349 patent – and the lower amount of 6,7-dimethoxy-quinoline-4-ol in Compound IB that is associated with the same. From there, it was a matter of admittedly "known" formulation techniques to achieve the claimed compositions.

Accordingly, Azurity respectfully requests that the Board cancel the claims under both §102 and §103.

II. STATE OF THE ART

A. Cabozantinib and Its Malate Salt

Exelixis markets cabozantinib (L)-malate under the tradenames CABOMETYX® and COMETRIQ® for the treatment of certain forms of cancer. Ex. 1005; Ex. 1006; Ex. 1007 ¶45. Cabozantinib (L)-malate (referred to as “Compound IB” in the ’349 patent) has the following structure:



Ex. 1007 ¶46.

Exelixis first disclosed cabozantinib in a different patent family claiming priority to 2003—well before the ’349 patent’s alleged priority date. Ex. 1008 at 199 (entry 12); Ex. 1007 ¶48. In that 2003 application, Exelixis admitted that oral administration was “preferable” and that capsules or tablets were suitable dosage forms when admixed with “customary excipients.” Ex. 1008 at 273:20-44;¹ Ex.

¹ Ex. 1008 is the 2009 patent that issued from the various applications that trace back to the 2003 application.

1007 ¶¶49-50. In this 2003-dated patent family, Exelixis specifically claimed cabozantinib as the free base “or a pharmaceutically acceptable salt thereof” along with its inclusion in a pharmaceutical composition with excipients. Ex. 1008 at claims 5-7; Ex. 1007 ¶51. Thus, nothing about cabozantinib, its pharmaceutically acceptable salts, or even its inclusion in a tablet or capsule pharmaceutical composition is novel. Ex. 1007 ¶51.

By the filing date of the ’349 patent, the (L)-malate salt of cabozantinib was also a known salt form. Ex. 1003 at Abstract; Ex. 1007 ¶52. Exelixis explained how to make this salt and two crystalline forms in Brown (Ex. 1003), which claims priority to 2009—prior to the ’349 patent’s earliest alleged priority date. Ex. 1003 at (30); Ex. 1007 ¶¶52-53. Indeed, Brown’s preparation of cabozantinib (L)-malate’s crystalline forms N-1 and N-2 is verbatim to that disclosed in the ’349 patent. *Compare* Ex. 1003 at [00115]-[00127] *with* Ex. 1001 at 29:40-30:60; Ex. 1027 ¶52. It was also found to contain a “de minimis” amount of a potentially genotoxic impurity—6,7-dimethoxy-quinoline-4-ol (*see* Ex. 1026 at 45, 53)—which is the only byproduct or contaminant mentioned in the ’349 patent.

Exelixis once again identified capsules and tablets as suitable pharmaceutical compositions for incorporating cabozantinib (L)-malate. Ex. 1003 at [0078]; Ex. 1007 ¶¶53-55. And Exelixis admitted that such pharmaceutical compositions could be prepared by “methods know[n] in the pharmaceutical formulation art.” Ex. 1003

at [0082]; Ex. 1007 ¶53. Thus, nothing about cabozantinib (L)-malate or its inclusion in a tablet or capsule with customary excipients is novel. Ex. 1007 ¶¶55-56.

B. Orally Administered Tablets and Capsules are Preferred Pharmaceutical Compositions

Active pharmaceutical ingredients (APIs) such as cabozantinib (L)-malate are almost always administered to a subject as part of a pharmaceutical composition. Ex. 1004 at 889, 891; Ex. 1007 ¶57. Oral administration is the most frequent route. Ex. 1004 at 889; Ex. 1034 at 442; Ex. 1007 ¶58. As compared against an injection, the oral route is simpler, more convenient, and ultimately safer for the patient. Ex. 1009 at 367; Ex. 1007 ¶59.

Tablets and capsules are the two most common oral dosage forms. Ex. 1009 at 367; Ex. 1004 at 889; Ex. 1034 at 442; Ex. 1007 ¶59. In fact, tablets were known to offer several advantages to both the manufacturer and the patient. Ex. 1004 at 889; Ex. 1034 at 442; Ex. 1007 ¶59. Manufacturing them is straightforward—a uniform powder is filled to a specified depth in the die of a press, compressed between two punches, and the tablet that forms is then ejected from the die. Ex. 1009 at 385; Ex. 1004 at 890-891; Ex. 1007 ¶60.

In addition to the API, tablets contain other substances referred to as “excipients.” Ex. 1004 at 891; Ex. 1007 ¶61. Certain classes/categories of excipients are normally incorporated into tablet formulations. Ex. 1004 at 891; Ex.

1007 ¶64. These categories include fillers, disintegrants, glidants, and lubricants, which are discussed in further detail below. Ex. 1004 at 891; Ex. 1007 ¶64.

1. Fillers

Fillers, which are also referred to as diluents, are a category of excipient that are added to the API in sufficient quantity to make a reasonably sized tablet. Ex. 1004 at 891; Ex. 1034 at 449; Ex. 1007 ¶65. This is particularly true for tablets that contain a low-amount of API. Ex. 1009 at 390; Ex. 1004 at 891; Ex. 1007 ¶65. Many excipients may be utilized as a filler. Ex. 1025 at 864; Ex. 1009 at 391 (Table 8); Ex. 1004 at 891; Ex. 1007 ¶¶66-67. However, microcrystalline cellulose is a very popular diluent that is usually used for preparing compressed tablets. Ex. 1004 at 891; Ex. 1009 at 391 (Table 8); Ex. 1007 ¶68.

2. Disintegrants

Disintegrants are a category of excipient that are added to tablets to “facilitate [their] breakup or disintegration after administration.” Ex. 1004 at 893; Ex. 1009 at 397; Ex. 1007 ¶69. Its inclusion promotes the rapid release of the API from the tablet. Ex. 1004 at 893; Ex. 1009 at 397; Ex. 1007 ¶69. Many excipients may function as a disintegrant. Ex. 1025 at 865; Ex. 1009 at 398 (Table 11); Ex. 1004 at 893; Ex. 1007 ¶¶70-71. However, super disintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone are now the most commonly used because they “display excellent disintegrant activity at low concentrations and

possess better compression properties” than other disintegrants. Ex. 1009 at 396; Ex. 1004 at 893; Ex. 1007 ¶72.

3. Glidants

Glidants are a category of excipient that are normally added to tablet formulations to enhance the flow of the powder into the tablet die for compression. Ex. 1009 at 388-89; Ex. 1004 at 893; Ex. 1007 ¶73. Inadequate flow can lead to manufacturing difficulties as well as the non-uniform production of tablets. Ex. 1007 ¶73. Many excipients may function as a glidant. Ex. 1025 at 868; Ex. 1009 at 389 (Table 7); Ex. 1007 ¶¶74-75. However, fumed silicon dioxide (i.e., colloidal silicon dioxide) is the most commonly used and effective glidant. Ex. 1009 at 390; Ex. 1004 at 893; Ex. 1025 at 185; Ex. 1034 at 452; Ex. 1007 ¶76.

4. Lubricants

Lubricants are a category of excipient that are normally added to tablet formulations to prevent adherence of the tablet to the die/punch. Ex. 1009 at 391-92; Ex. 1004 at 892-893; Ex. 1007 ¶77. Many excipients may function as a lubricant. Ex. 1025 at 873; Ex. 1009 at 392 (Table 9); Ex. 1004 at 892; Ex. 1007 ¶¶78-80. However, magnesium stearate and stearic acid are two of the more widely used lubricants. Ex. 1004 at 892-893; Ex. 1009 at 392; Ex. 1025 at 697; Ex. 1007 ¶80.

III. THE CHALLENGED CLAIMS ARE UNPATENTABLE

Azurity requests cancellation of claims 1-3.

A. Grounds of Challenges

IPR is requested for the following grounds:

Ground	Basis	Challenged Claims
1	Anticipation by U.S. 9,717,720 (“Wilson”)	1-3
2	Obviousness over WO 2010/083414 (“Brown”) in view of U.S. 7,169,789 (“Kubo”) and Remington: The Science and Practice of Pharmacy (“Remington”)	1-3

B. The Prior Art

All asserted references are §102(a)(1) prior art in view of the effective filing date of the Challenged Claims, February 8, 2021, discussed *infra*. Should the Board disagree with Petitioner’s analysis in Ground 1, then Brown is prior art under §102(a) and both Kubo and Remington are prior art under §102(b).

Reference	Publication	Exhibit No.
1. U.S. 9,717,720 (“Wilson”)	2017	Ex. 1002
2. WO 2010/083414 (“Brown”)	2010	Ex. 1003
3. U.S. 7,169,789 (“Kubo”)	2007	Ex. 1028
4. Remington: The Science and Practice of Pharmacy (“Remington”)	2005	Ex. 1004

The accompanying declarations of Dr. Graham Buckton (Ex. 1007) and Dr. William Dichtel (Ex. 1027) support this Petition.

IV. LEVEL OF ORDINARY SKILL IN THE ART

Exelixis previously proposed a person of ordinary skill in the art (“POSA”) would have had at least a bachelor’s degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. Ex. 1010 ¶11. This definition has been utilized. Ex. 1007 ¶31; Ex. 1027 ¶¶24, 27.

V. CLAIM CONSTRUCTION

Claims are construed using the same standard that would be used in a civil action under 35 U.S.C. §282(b). 37 C.F.R. §42.100(b). The Board need only construe claims to the extent necessary to resolve controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). For the Board’s clarity, Azurity sets forth the specification’s express definition of the impurity limitation recited in claim 1 and the construction of the impurity limitation recited in claim 3 applied in an district court litigation.

A. Claim 1 – “essentially free of process byproducts or contaminants”

The phrase “essentially free of process byproducts or contaminants” is expressly defined. Ex. 1001 at 8:15-20 (“‘Essentially free’ as used in the phrase

‘essentially free of process byproducts or contaminants,’ means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.”); Ex. 1007 ¶36. This definition has been applied in this petition. Ex. 1007 ¶36.

B. Claim 3 – “essentially free of 6,7-dimethoxy-quinoline-4-ol”

There is no express definition of “essentially free of 6,7-dimethoxy-quinoline-4-ol” in the ’349 patent. Outside of claim 3, the ’349 patent does not utilize this phrase. However, the ’349 patent does identify “6,7-dimethoxy-quinoline-4-ol” as “a byproduct that may form during the synthesis of Compound IA or IB” and is to be minimized in pharmaceutical compositions. Ex. 1001 at 22:22-27. Further, in prior litigation, the district court applied a numerical limit of 200 ppm or less for the potentially genotoxic impurity, 6,7-dimethoxy-quinoline-4-ol. Ex. 1026 at 45. Solely for purposes of this petition, Azurity does not contest the accuracy of this construction and has applied it in this petition. Ex. 1007 ¶37.

VI. GROUND 1: ANTICIPATION BY WILSON

A. Wilson is Prior Art to the Challenged Claims

Although Wilson (Ex. 1002) is in the same patent family as the ’349 patent—and contains an anticipatory species of the broadly Challenged Claims—it and all of the other applications in the ’349 patent’s priority claim fail to afford written description support for the Challenged Claims. As explained below, they are only

entitled to their actual filing date of February 8, 2021. Ex. 1007 ¶¶81-122. As such, Wilson is anticipatory prior art. Ex. 1007 ¶¶122-162.

1. No presumption of an earlier priority date

The effective filing date of the Challenged Claims was never considered during prosecution. Ex. 1014 at 57-99; Ex. 1007 ¶¶83-86. Thus, there is no presumption that the Challenged Claims are entitled to the priority date of any earlier-filed application. *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015); *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008) (“When neither the PTO nor the Board has previously considered priority,” there is no presumption that claims “are entitled to the effective filing date of an earlier filed application.”). Accordingly, Exelixis has the burden to establish that the Challenged Claims were described as of any earlier priority date. *Dynamic Drinkware*, 800 F.3d at 1380. Absent specific evidence of entitlement to an earlier priority date, the Challenged Claims must be assigned their actual filing date of February 8, 2021. *Id.*

To establish an earlier priority date, each earlier application in the priority chain must fully disclose the claimed invention by meeting all requirements of 35 U.S.C. §112. *See In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011). Likewise, to claim priority to an earlier provisional application, the provisional must disclose the claimed invention by meeting §112 requirements. 35 U.S.C. §119(e)(1);

Dynamic Drinkware, 800 F.3d at 1378. The test for sufficiency under the written description requirement “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).

Exelixis cannot meet its burden for the Challenged Claims. A sufficient written description must “support[] all the limitations.” *Technology v. Videotek*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). Yet, if a claim includes more than what the parent application described, encompassing a broader invention, it is no longer entitled to an earlier effective filing date. *See Rsch. Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 871-72 (Fed. Cir. 2010); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159-60 (Fed. Cir. 1998) (same). “Entitlement to a filing date extends only to subject matter that is disclosed; not to that which is obvious.” *Rsch. Corp.*, 627 F.3d at 870.

2. Exelixis’s broad claims make compliance with the written description requirement impossible

The Challenged Claims all require the inclusion of “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” in a tablet/capsule composition having less than 200 ppm of “process byproducts or contaminants” (claim 1) or less than 200 ppm of “6,7-dimethoxy-quinoline-4-ol” (claims 2 and 3). Ex. 1001 at 34:5-51. Thus, to satisfy the written description requirement, the priority applications must convey possession of the full scope of

the Challenged Claims – including the innumerable permutations of excipients within a composition that achieves impurity levels below 200 ppm. *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1384 (Fed. Cir. 2019) (“[W]hen the inventor expressly claims [a certain] result, our case law provides that [such] result must be supported by adequate disclosure in the specification.”). Exelixis’s prior admissions render this impossible.

Exelixis admitted—in a litigation involving the ’349 patent—that the purity of the composition can be impacted by the interaction of Compound IB with excipients in the composition; that those interactions are unpredictable; and that none of this knowledge was in the prior art.² However, the ’349 patent attempts to

² See Ex. 1019 at 712:19-713:2 (Exelixis expert answering “No, because as we’ve seen, the process of blending with excipients and making it into the drug product can result in increase in the [6,7-dimethoxy-quinoline-4-ol] 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”); *id.* at 729:12-731:2 (Exelixis expert discussing important properties for formulating cabozantinib (L)-malate); *id.* at 739:3-740:5 (Exelixis expert indicating that to formulate cabozantinib (L)-malate into a drug product that was ‘essentially free’ of the claimed impurity one “would have to know about [the API’s] chemical stability . . . you would also have

claim endless combinations and permutations of excipients with Compound IB and the purity limitation. Given the unknown interactions, and impurity-producing impacts, of these countless excipients, Patentee's attempt to claim the universe is not justified. Neither the specification in the '349 Patent, nor any of its progenitor applications, provide sufficient information to justify a claim so broad. Ex. 1007 ¶¶87-122. Thus, Exelixis failed to provide a written description of those excipients and manufacturing conditions that were needed to obtain compositions having the

to know the list of physicochemical properties I mentioned before, including the excipient compatibility studies"); 739:3-740:5 (Exelixis expert admitting that none of these properties were known in the prior art); Ex. 1018 at 55 ("[A]chieving API with the claimed purity does not mean that any resulting formulation would have necessarily had the same purity."); Ex. 1013 at ¶68 ("Achieving API essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity does not necessitate that a formulation of that API would be similarly pure."); Ex. 1019 at 712:15-713:14 (same); Ex. 1019 at 733:15-734:13 (Exelixis expert testifying to unpredictability); Ex. 1019 at 773:5-24 (Exelixis's expert admitting that "[o]ther than disclosing a synthetic process that makes an API exceptionally low, [the '349 patent] doesn't then have an additional – anything additional that would control for [6,7-dimethoxy-quinoline-4-ol]"); Ex. 1007 ¶87.

requisite purity. *See, e.g., Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (“No written description can be found when “a POSA is deprived of any meaningful guidance into what [compositions] beyond the examples and formulas, if any, would provide the same result” as the claimed compositions.”); *Ariad*, 598 F.3d at 1352 (“[W]hen a patent claims a genus by its function or result, the specification [must] recite[] sufficient materials to accomplish that function.”); *Abbvie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (“[T]he specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.”); *In re Curtis*, 354 F.3d 1347, 1358 (Fed. Cir. 2004) (“[A] patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when, as is the case here, the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.”); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (“Claiming all DNA[s] that achieve a result without defining what means will do so is not in compliance with the description requirement; it is an attempt to preempt the future before it has arrived.”); *Juno Therapeutics, Inc. v. Kite Pharma.*, 10 F.4th 1330, 1339-40 (Fed. Cir. 2021) (“But the written description of the ’190 patent discloses only two scFv examples and provides no details regarding the

characteristics, sequences, or structures that would allow a person of ordinary skill in the art to determine which scFvs will bind to which target. That scFvs in general were well-known or have the same general structure does not cure that deficiency.”); *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345-46 (Fed. Cir. 2005) (finding no support for a broader claim, the Federal Circuit stated: “[a]fter reading the patent, a person of skill in the art would not understand how to make a seamless DWT generically and would not understand LizardTech to have invented a method for making a seamless DWT, except by [one single route] of ‘maintaining updat[ed] sums of DWT coefficients.’”); *In re Grimme*, 274 F.2d 949, 952 (CCPA 1960) (“The questions as to the sufficiency of disclosure to support a generic or subgeneric claim in the field of chemistry has frequently been considered by this court and it has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group.”); M.P.E.P. §2163 (“Guidelines”) (collecting cases on compliance with the written description requirement).

3. The ’349 patent’s “priority” applications do not convey possession of the breadth of the Challenged Claims

a. The ’520 provisional does not disclose any compositions

The ’520 provisional “relates to methods of preparing compounds useful for modulating kinase enzymatic activity.” Ex. 1015 at [0001]; Ex. 1007 ¶91. No pharmaceutical compositions or excipients are mentioned. Ex. 1007 ¶91. There is

no discussion of “process byproducts or contaminants” or the identification of 6,7-dimethoxy-quinoline-4-ol as a process byproduct or contaminant. Ex. 1007 ¶91. Accordingly, the ’520 provisional provides no written description support for the Challenged Claims. Ex. 1007 ¶92.

b. The ’527 provisional omits pertinent limitations

The ’527 provisional relates to “[p]harmaceutical compositions and unit dosage forms.” Ex. 1016 at Abstract; Ex. 1007 ¶93. However, there is no discussion of “process byproducts or contaminants;” no mention of compositions that are “essentially free” of such compounds; and no mention of any 200 ppm impurity limit. Ex. 1016; Ex. 1007 ¶95. There is no mention of the generalized categories of “filler,” “disintegrant,” “glidant,” or “lubricant” as claimed. Ex. 1007 ¶95. Rather, there is only a single reference to the concept of an “excipient”:

Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are disclosed in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. *The amount of*

carriers and excipients used in a composition can be varied according to the amount of active ingredient used (that is, Compound I).³

Ex. 1016 at [0018]; Ex. 1007 ¶96. Yet by this paragraph’s own terms, this omnibus catch-all is limited to “Compound I” as the active ingredient rather than “Compound IB” as required by the Challenged Claims. *Id.*; Ex. 1007 ¶96.

Furthermore, a “carrier” is not co-extensive with the Challenged Claims’ requirement of “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants.” Ex. 1016 at [0018]; *id.* at [0009]-[0015] (reciting “a pharmaceutically acceptable carrier”); Ex. 1007 ¶97. It is not even clear from this catch-all whether the category of “carriers” is inclusive or exclusive of the category of “excipients.” Ex. 1016 at [0018] (referring to “carriers and excipients used in a composition”); Ex. 1007 ¶97. Thus, broadly referencing “[v]arious carriers,” “carriers and excipients,” or even pointing to a potential “laundry list” of carriers is certainly not a blaze mark directing one to the selection and inclusion of each of the categories of “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” as the Challenged Claims require. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) (“In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy

³ Unless otherwise indicated, all bold emphases are added.

the written description requirement....”); Ex. 1007 ¶¶97. Nor does such a catch-all convey anything regarding whether any composition exhibits the requisite purity that is expressly claimed. *Nuvo*, 923 F.3d at 1384; Ex. 1007 ¶¶98. Accordingly, the ’527 provisional fails to provide any written description support for the Challenged Claims. Ex. 1007 ¶¶99.

c. The ’559 application fails to convey possession

The ’559 application is the earliest non-provisional application in the ’349 patent’s family. Ex. 1001 at (60). Like the provisional applications before it, the ’559 application fails to afford written description support for the Challenged Claims. Ex. 1007 ¶¶100-116.

The ’559 application contains only two instances in which the phrase “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” appears. Ex. 1017 at [00104]-[00109] and [00127]-[00132]; Ex. 1007 ¶¶101-104. But usage alone is insufficient. *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (“An *ipsis verbis* disclosure of a claimed genus ... is not *per se* sufficient to meet the written description requirement.”). Even if it were, any such reliance is rebutted by the accompanying description’s clarification that particular excipients were being referenced. Ex. 1017 at [00104]-[00109] and [00127]-[00132]; Ex. 1007 ¶¶101-104. In full context, the first instance states:

[00104] 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.*

[00105] *In this embodiment, the filler comprises microcrystalline cellulose.*

[00106] *In this embodiment, the disintegrant comprises croscarmellose sodium.*

[00107] *In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.*

[00108] *In this embodiment, the glidant comprises fumed silica.*

[00109] *In this embodiment, the lubricant comprises stearic acid.*

Ex. 1017 at [00104]-[00109]; Ex. 1007 ¶102. Accordingly, the specification *immediately limits* the species of filler, disintegrant, glidant, and lubricant that Applicant possessed “[i]n this embodiment” despite what was otherwise broadly worded. Ex. 1007 ¶102. This does not provide written description for any excipient in these categories—particularly where the overall composition must possess a specified purity level. *Tronzo*, 156 F.3d at 1158-60; *Nuvo*, 923 F.3d at 1384; Section VI.A.2, *supra* (collecting cases); Ex. 1007 ¶102.

The second instance where the ’559 application mentions the phrase “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” limits each category to a particular excipient in identical fashion. Ex.

1017 at [00127]-[00132]; Ex. 1007 ¶¶103-104. Again, this is not sufficient for written description of a broader genus claim to all excipients.

Thus, not only does the '559 application's usage of "one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants" fail to convey possession of such an unrestricted invention, it undermines any such assertion of written description support by expressly limiting the embodiment to very specific species of excipients described as present "*[i]n this embodiment*"—and not all excipients falling within the broader categories. Ex. 1007 ¶¶101-104.

d. Other generalized disclosures in the '559 application do not provide support for the Challenged Claims

The remainder of the '559 application's description fails to lend any further support to the Challenged Claims. Ex. 1007 ¶¶105-116. Consider the following uninformative passage from the '559 application:

the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various 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....

Ex. 1017 at [0096]; Ex. 1007 ¶106. Such general statements—a generic laundry list—do not convey possession of the Challenged Claims. *See, e.g., Fujikawa*, 93 F.3d at 1571 ("Clearly, however, just because a moiety is listed as one possible

choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be....”); Ex. 1007 ¶106. The absence of possession is even more glaring when considering the additional purity requirement that must be exhibited by the composition produced by the combination of laundry-listed ingredients in what Exelixis has characterized as unpredictable formulation arts. *See* Section VI.A.2, *supra*.

e. Species in the ’559 application do not convey possession of broader claims

Sufficiently describing the categories of filler, disintegrant, glidant, and lubricant requires either (1) “a representative number of species falling within the scope of the genus” or (2) “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 (internal quotation marks omitted). It is imperative to do so when claiming a result to be achieved, such as the Challenged Claims’ expressly recited purity limitation. Section VI.A.2, *supra*. The ’559 application’s narrow disclosure of excipient species fails to meet the requirement. Ex. 1007 ¶¶108-116.

The only evidence in the ’559 application for a POSA to evaluate any disclosed composition’s satisfaction of the purity limitation is provided in Tables 7A-7B and 8A-8B for two capsule formulations. Ex. 1017 (’559 application) at

[00161]-[00163]; Ex. 1007 ¶109.⁴ The excipients in these two capsules are virtually identical. Ex. 1007 ¶¶88-89, 110-111. No information can be extrapolated from this data regarding the selection of any other excipient—as Exelixis and its experts have admitted. Ex. 1019 at 712:15-713:14, 730:16-20, 733:9-14, 733:21-734:13; Ex. 1007 ¶¶110-111; Section VI.A.2, *supra*.

Moreover, within each of the categories of filler, disintegrant, glidant, and lubricant, there are many members having obvious chemical/physical distinctions (e.g., ionic vs. nonionic compounds; inorganic vs. organic compounds; sugars vs. acids vs. esters vs. polymers). Ex. 1007 ¶¶112-116. There are no common structural features within each category. *Id.* Similarly, one member of a category is not representative of other members of the same category (or of their expected behaviour in a given composition). *Id.* And the specification in the '559 application provides **no** guidance as to what chemical categories of excipients, if any, would minimize or

⁴ Although two additional capsule compositions were provided in [0025]-[0026], they contain the same excipients as in [00161]-[00163] and were not evaluated for purity. Similarly, three tablet compositions were provided in [0020]-[0022]. Two of which do not contain “Compound IB” and none were evaluated for purity. Accordingly, these compositions provide no useful information regarding compliance with the written description requirement. Ex. 1007 ¶109, n.8.

eliminate the formation of “byproducts and contaminants.” Ex. 1007 ¶116. Nor does the ’559 application provide any evidence of tablets that would do so. *Id.*

Accordingly, nothing about the ’559 application’s selection of one excipient from one category would allow a POSA to navigate or visualize any alternative selections in view of the explicitly recited purity limitation. Ex. 1007 ¶¶112-116. There are simply no “blaze marks” to guide a POSA to the members of the excipient categories that will afford the claimed purity. *Regents of the Univ. of Minn. v. Gilead Scis., Inc.*, 61 F.4th 1350, 1358 (Fed. Cir. 2023).

f. The ’716, ’653, ’323, and ’394 applications fail to afford any additional written description support

The ’349 patent also claims the benefit of priority through each of the ’716 application (Ex. 1020), the ’653 application (Ex. 1021), the ’323 application (Ex. 1022), and the ’394 application (Ex. 1023). Ex. 1001 at (60); Ex. 1007 ¶117. Aside from updating the priority claim, the written description of these applications are identical. Ex. 1020 at 10-60; Ex. 1021 at 10-60; Ex. 1022 at 10-63; Ex. 1023 at 28-74; Ex. 1007 ¶117. Moreover, no preliminary amendments to the claims were simultaneously filed with the applications (as a potential source of new matter). Ex. 1020 at 57-60; Ex. 1021 at 59-60; Ex. 1022 at 61-63; Ex. 1023 at 2-3, 15-17; Ex. 1007 ¶117. Accordingly, none of these applications offer any additional written description support to the Challenged Claims. Ex. 1007 ¶118.

B. The Effective Filing Date of the Challenged Claims Can Only Be February 8, 2021

The '349 patent issued from the '275 application (Ex. 1014), which was filed on February 8, 2021. Ex. 1001 at (21)-(22). With the filing of the '275 application, Exelixis submitted a preliminary amendment that cancelled claims 1-34 and added new claims 35-37. Ex. 1014 at 57-60; Ex. 1007 ¶¶83, 119.

The remarkable expansion of the scope of the claim that occurred with the February 8, 2021 preliminary amendment becomes clear upon inspection of the “composition” claims that were cancelled. *Compare* Ex. 1014 at 47-55 *with* Ex. 1014 at 58; Ex. 1007 ¶¶119-120. All of those claims recited very narrow formulations with very specific excipients. *Id.*; Ex. 1007 ¶119. As but one example, consider cancelled claim 26, with its identification of excipients and recitation of amount to the hundredth of a decimal place:

26. A pharmaceutical composition according to Table 5.

Table 5

	mg/unit dose
Ingredient	50mg
Compound IB (10 % drug load as Compound IA)	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

Ex. 1014 at 54; Ex. 1007 ¶119. Substituted for these narrow claims are the Challenged Claims. Unlike their predecessors, the Challenged Claims recite no specific excipients at all—claiming entire, broad categories of excipients and innumerable combinations and permutations of these excipients. Ex. 1014 at 58; Ex. 1007 ¶120.

Indeed, the preliminary amendment 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). Ex. 1007 ¶¶121-122. As such, the addition of new claim 35 must be considered new matter, meaning that the Challenged Claims are not entitled to a priority date any earlier than February 8, 2021. *Nat. Alternatives Int’l, Inc. v. Iancu*, 904 F.3d 1375, 1383 (Fed. Cir. 2018) (“Claims reciting new matter, however, are entitled to only the filing date of the CIP application and not to the filing date of the earlier-filed application.”); M.P.E.P. §2163 (“Guidelines”) (discussing failure to comply with the written description requirement for “New or Amended Claims”).⁵

⁵ Azurity reserves the right to contest any remaining issues concerning compliance with the written description requirement by the ’349 patent itself in the appropriate forum.

Accordingly, Wilson (Ex. 1002) is prior art to the Challenged Claims. Ex. 1007 ¶¶122-123.

C. Wilson Discloses a Species that Anticipates the Broad Genus Claims of the '349 Patent

As shown below, Wilson (Ex. 1002) discloses a particular capsule composition (i.e., a species) that falls within the broad genus claims of the '349 patent. Ex. 1007 ¶¶125-162. Thus, Wilson anticipates each claim. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

1. Claim 1

Limitations	Wilson's Disclosure
A pharmaceutical composition for oral administration comprising Compound IB;	Wilson discloses a “pharmaceutical composition for oral administration....” Ex. 1002 at 5:36-38, 32:24-40; Ex. 1007 ¶¶126-129.
[chemical structure of “IB” omitted]	Wilson discloses incorporating “Compound IB” in a pharmaceutical composition. Ex. 1002 at 32:24-40; Ex. 1007 ¶¶130-132.
one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants,	In the same passage that discloses “Compound IB” in a pharmaceutical composition, Wilson also discloses a filler (“microcrystalline cellulose”), a disintegrant (“croscarmellose sodium and sodium starch glycolate”), a glidant (“fumed silica”), and a lubricant (“stearic acid”) in that same pharmaceutical composition. Ex. 1002 at 32:24-40; Ex. 1007 ¶¶133-144.

wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition,	Wilson discloses a “pharmaceutical capsule composition,” which is intended for oral administration. Ex. 1002 at 32:24-40; Ex. 1007 ¶145.
and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.	Wilson indicates that “6,7-dimethoxy-quinoline-4-ol” is a type of contaminant or byproduct. Ex. 1002 at 21:63-22:14; Ex. 1007 ¶146. Wilson monitored the capsule composition reported in Table 3 for the presence/formation of 6,7-dimethoxy-quinoline-4-ol and provided the results in Tables 7A-7B. Ex. 1002 at 32:24-33:40; Ex. 1007 ¶147. Wilson states “that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.” Ex. 1002 at 34:62-65; Ex. 1007 ¶147. Thus, Wilson discloses a species of formulation that is “essentially free of process byproducts or contaminants.” Ex. 1007 ¶148.

2. Claim 2

Limitations	Wilson’s Disclosure
The pharmaceutical composition of claim 1	See discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶¶149-150.
wherein the process byproduct or contaminant is 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition.	See discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶¶149-150.

3. Claim 3

Limitations	Wilson’s Disclosure
A pharmaceutical composition for oral administration comprising Compound IB;	<i>See</i> discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶155.
[chemical structure of “IB” omitted]	<i>See</i> discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶156.
one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants,	<i>See</i> discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶¶157-160.
wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition,	<i>See</i> discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶161.
and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy- quinoline-4-ol.	<i>See</i> discussion of Wilson’s disclosures that anticipate Claim 1 in Section VI.C.1, <i>supra</i> ; Ex. 1007 ¶162.

VII. GROUND 2: OBVIOUSNESS OVER BROWN IN VIEW OF KUBO AND REMINGTON

Patent claims may simultaneously lack the required written description support to entitle them to priority (Ground 1) and still be obvious in view of the prior art (Ground 2). *Tronzo*, 156 F.3d at 1158 (“A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement.”); *Ex parte Kubin*, 2007 Pat. App. LEXIS 13, *9-

10, 83 U.S.P.Q.2D (BNA) 1410, 1413-1414 (Bd. Pat. App. & Interferences May 31, 2007). That is the case here.

The Challenged Claims would have been obvious over Brown (Ex. 1003) in view of Kubo (Ex. 1028) and Remington (Ex. 1004). Brown (Ex. 1003) in view of Kubo (Ex. 1028) teaches the synthetic approach of the '349 patent. Thus, to the extent the '349 patent affords cabozantinib (L)-malate containing “less than 200 ppm” of impurity, then the prior art must do so as well. Moreover, Brown teaches the preparation of tablet and capsule compositions of Compound IB while pointing to Remington (Ex. 1004) for “known” formulation methods. Between Brown and Remington, a POSA would have been directed to not only prepare the claimed compositions, but to do so using the very excipients identified in the '349 patent's working examples. Accordingly, the Challenged Claims and their recited purity limitations would have been obvious.

A. Introduction to Brown

Brown is entitled “Malate Salt of [Cabozantinib], and Crystalline Forms Thereof for the Treatment of Cancer.” Brown provides a synthesis for cabozantinib (L)-malate, a quinoline-containing antitumor compound, and describes the preparation of two crystalline forms (denoted N-1 and N-2). Ex. 1003 at [0098]-[00134]; Ex. 1027 ¶¶39, 42. Brown also describes the preparation of pharmaceutical compositions of cabozantinib (L)-malate in conjunction with a pharmaceutically

acceptable excipient. Ex. 1003 at [0066], [0078]; Ex. 1007 ¶¶164-165. Regarding the preparation of such compositions, Brown explains:

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

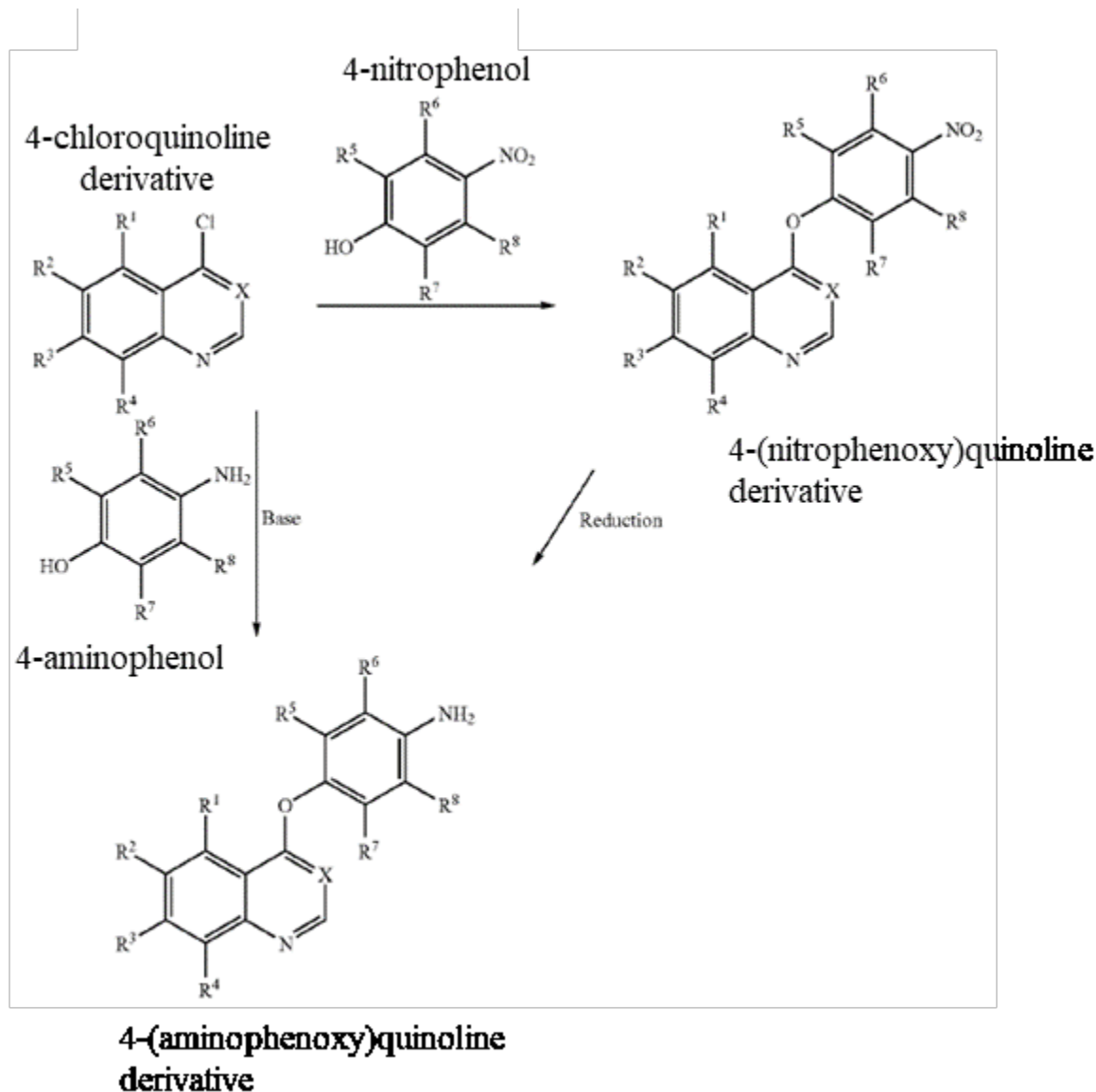
Brown at [0082]; Ex. 1007 ¶165. Thus, not only does Brown disclose cabozantinib (L)-malate, but it also teaches the preparation of capsules and tablets containing excipients such as fillers, disintegrants, and lubricants. Ex. 1007 ¶¶165-166.

Additionally, Brown also directs a reader to “known” methods for preparing pharmaceutical compositions as discussed in Remington—just like the ’349 patent. Ex. 1001 at 20:38-52; Ex. 1007 ¶¶167, 211-212.

B. Introduction to Kubo

Kubo is entitled “Quinoline Derivatives and Quinazoline Derivatives.” Kubo relates to the synthesis of antitumor quinoline compounds—just like Brown and the ’349 patent. Ex. 1028 at 1:7-13 (“[T]he present invention relates to quinoline derivatives and quinazoline derivatives that are useful for the treatment of diseases such as tumor...”); Ex. 1003 at [0010], [0012] (identifying the quinoline derivative cabozantinib and its malate salts for treating “cancer”); Ex. 1001 at 1:29-32 (“More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death...”); Ex. 1027 ¶42.

Kubo describes two alternative approaches for preparing a 4-aminophenoxy-quinoline beginning with a 4-chloroquinoline starting material:



Ex. 1028 at 12:46-14:4 (Annotated); Ex. 1027 ¶¶45. The first alternative is analogous to Brown's synthesis, which utilizes a two-step reaction sequence to afford a 4-(aminophenoxy)quinoline derivative. Ex. 1028 at 12:46-55; Ex. 1027 ¶¶44-47. Kubo's second alternative is analogous to the '349 patent, which utilizes a one-step reaction sequence to afford the same 4-(aminophenoxy)quinoline derivative. Ex. 1028 at 12:55-59; Ex. 1027 ¶¶48.

C. Introduction to Remington

Remington is entitled “Remington: The Science and Practice of Pharmacy.” Remington is a “treatise on the theory and practice of the pharmaceutical sciences” that is intended to be a reference for “practitioners of the pharmaceutical and medical sciences.” Ex. 1004 at 5; Ex. 1007 ¶168. Accordingly, Remington would be the type of reference a POSA would consult to understand “known” methods of preparing pharmaceutical compositions. Ex. 1007 ¶168. This would be particularly true for a POSA reading Brown (which cites to the 18th edition of Remington for “known” methods). Ex. 1003 at [0082]; Ex. 1007 ¶168.

Remington explains that “[d]rug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules.” Ex. 1004 at 889; Ex. 1007 ¶169. Tablets, in particular, “have been in widespread use since the latter part of the 19th century, and their popularity continues.” *Id.* Remington also explains that some types of excipients are normally incorporated into a tablet formulation, such as “diluent, binders, glidants, and lubricants,” because they “help to impart satisfactory processing and compression characteristics to the formulation.” Ex. 1004 at 891; Ex. 1007 ¶170. Other excipients, such as “disintegrants,” are included because they “help[] to give additional desirable physical characteristics to the finished tablet.” Ex. 1004 at 891; Ex. 1007 ¶170. Remington also directs a POSA to the particular excipients set forth in the ’349

patent’s working example of a capsule composition containing less than 200 ppm of “6,7-dimethoxy-quinoline-4-ol,” as discussed in further detail below.

D. Brown in view of Kubo and Remington Render the Challenged Claims Obvious

1. Claim 1

a. Preamble

Claim 1’s preamble recites: “A pharmaceutical composition for oral administration...” Should the Board find that this preamble is limiting, Brown discloses such a “pharmaceutical composition.” Ex. 1003 at [0002]-[0003], [0013]-[0014], [0066], [0078], [0082] and [0087]; Ex. 1007 ¶¶172-173.

b. Compound IB

Claim 1’s composition requires “Compound IB.” Compound IB is cabozantinib (L)-malate. Ex. 1007 ¶174; Ex. 1027 ¶34. Brown teaches the inclusion of cabozantinib (L)-malate (i.e., “Compound IB”) in a pharmaceutical composition. Ex. 1003 at [0002], [0051]-[0052], [0054], [0066], [0077]-[0078], claim 11; Ex. 1007 ¶174.

A POSA would have been motivated to select cabozantinib (L)-malate for inclusion in a pharmaceutical composition. Ex. 1007 ¶175. Brown explains that cabozantinib (L)-malate “exhibit[ed] beneficial properties over the free base and other salts....” Ex. 1003 at [0053]; Ex. 1007 ¶175. Brown further taught that cabozantinib (L)-malate had “a preferred combination of pharmaceutical properties

for development,” such as its chemical/physical stability and solubility. Ex. 1003 at [0051]-[0054]; Ex. 1007 ¶175. Moreover, Exelixis previously agreed that a POSA would be so motivated. Ex. 1026 at 54 (“The parties agree that a POSA would be motivated to formulate the cabozantinib (L)-malate API as a capsule or tablet....”).

A POSA would have also had a reasonable expectation of successfully including cabozantinib (L)-malate in a pharmaceutical composition. Ex. 1007 ¶176; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise given its reliance on “known” methods/techniques in both Brown and the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

c. Fillers

Claim 1’s composition requires “one or more fillers.” Brown teaches the inclusion of “fillers.” Ex. 1003 at [0082]; Ex. 1007 ¶178. Remington also teaches that fillers (i.e., “diluent”) are added to tablet formulations to facilitate manufacturing. Ex. 1004 at 891; Ex. 1007 ¶179. Moreover, Remington says it is “obvious” to include a filler “to make tableting possible.” Ex. 1004 at 891; *see also* Section II.B.1, *supra*. Given Brown’s teaching that compositions may include as little as 1% of cabozantinib (L)-malate, a POSA would have recognized that it would be necessary to include a filler. Ex. 1003 at [0078]; Ex. 1007 ¶179. Exelixis cannot contend otherwise—it previously agreed that a POSA would be motivated to include a “filler” and the district court found the same. Ex. 1026 at 54 (“The parties agree

that a POSA would be motivated to formulate the cabozantinib (L)-malate API as a capsule or tablet and ensure the final formulation meets the ‘compositional limitation.’”); *id.* at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that includes a filler....”).

Remington further teaches that microcrystalline cellulose “usually is used as an excipient in direct-compression formulas.” Ex. 1004 at 891; Ex. 1025 at 130 (“Microcrystalline cellulose is widely used in pharmaceuticals....”); Ex. 1007 ¶180. A POSA would have been motivated to select microcrystalline cellulose for use as the filler because, popularity aside, it exhibits “excellent compressibility.” Ex. 1009 at 391; Ex. 1007 ¶180. Accordingly, a POSA would have been motivated to include microcrystalline cellulose as the “filler” in a tablet composition.

A POSA would have had a reasonable expectation of successfully utilizing one or more “fillers” such as microcrystalline cellulose to prepare a tablet composition in view of Remington’s express teachings, noted above. Ex. 1007 ¶181; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise given its reliance on “known” methods/techniques in both Brown and the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

d. Disintegrants

Claim 1’s composition requires “one or more disintegrants.” Brown teaches the inclusion of “disintegrants” in the pharmaceutical compositions. Ex. 1003 at

[0082]; Ex. 1007 ¶183. Remington teaches that disintegrants are “added to a tablet to facilitate its breakup or disintegration after administration.” Ex. 1004 at 893; Ex. 1007 ¶184. Including a disintegrant facilitates efficient release of the active ingredient from the tablet and allows for its rapid dissolution. *Id.*; *see also* Section II.B.2, *supra*. Accordingly, a POSA would have been motivated to include a “disintegrant” in the tablet composition. Exelixis cannot contend otherwise—it previously agreed that a POSA would be motivated to include a “disintegrant” and the district court found the same. Ex. 1026 at 54; *id.* at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that includes a ... disintegrant....”).

Additionally, a POSA would have found it obvious to include a particular species of disintegrant in the tablet formulation. Brown identified “croscarmellose sodium” as an example of a disintegrant to include in its solid dosage forms. Ex. 1003 at [0082]; Ex. 1007 ¶185. Croscarmellose is known as a “super disintegrant,” which is a type of material that Remington identifies as having gained in popularity for use as disintegrating agent. Ex. 1004 at 893; Ex. 1007 ¶185. Remington further teaches that croscarmellose is a “more efficient” disintegrant than other super disintegrants. *Id.* Thus, popularity aside, a POSA would have been motivated to select croscarmellose sodium for inclusion as a disintegrant in view of Brown and Remington. Ex. 1007 ¶185.

A POSA would have had a reasonable expectation of successfully utilizing one or more “disintegrants” such as croscarmellose sodium in view of Brown’s and Remington’s express teachings, noted above. Ex. 1007 ¶186; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise given its reliance on “known” methods/techniques in both Brown and the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

e. Glidants

Claim 1’s composition requires “one or more glidants.” Remington teaches that “glidants” are added to tablet formulations in order to improve flow characteristics. Ex. 1004 at 893; Ex. 1007 ¶188. In fact, it was common knowledge to add a glidant as a manufacturing aid. *See* Section II.B.3, *supra*. Accordingly, a POSA would have been motivated to include a “glidant” in the tablet composition. Exelixis cannot contend otherwise—it previously agreed that a POSA would be motivated to include a “glidant” and the district court found the same. Ex. 1026 at 54; *id.* at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that includes a ... glidant.”).

Additionally, a POSA would have found it obvious to include a particular species of glidant in the tablet formulation. Remington indicates that “[c]olloidal silicon dioxide Cab-o-sil (*Cabot*) is the most commonly used glidant....” Ex. 1004 at 893; Ex. 1025 at 186 (“Colloidal silicon dioxide is widely used in

pharmaceuticals....”); Ex. 1007 ¶188. “Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.” Ex. 1025 at 186; Ex. 1007 ¶189. Thus, a POSA would have been motivated to select colloidal silicon dioxide as a glidant to improve facilitate tableting. Ex. 1007 ¶189.

A POSA would have had a reasonable expectation of successfully utilizing one or more “glidants” such as colloidal silicon dioxide in view of Remington’s express teachings, noted above. Ex. 1007 ¶190. Exelixis cannot contend otherwise given its reliance on “known” methods/techniques in both Brown and the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

f. Lubricants

Claim 1’s composition requires “one or more lubricants.” Brown teaches the inclusion of “lubricants” in the pharmaceutical compositions. Ex. 1003 at [0082]; Ex. 1007 ¶192. Remington explains that “[l]ubricants have a number of functions in tablet manufacture” because they prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, [and] facilitate the ejection of the tablets from the die cavity....” Ex. 1004 at 892; Ex. 1007 ¶193; *see also* Section II.B.4, *supra*. Moreover, Remington explains that “most tablets have the tendency to expand and will bind and stick to the side of the die.” *Id.* However,

“[t]he choice of the proper lubricant will overcome this effectively.” *Id.* Accordingly, a POSA would have been motivated to include a “lubricant” in the tablet composition. Exelixis cannot contend otherwise—it previously agreed that a POSA would be motivated to include a “lubricant” and the district court found the same. Ex. 1026 at 54; *id.* at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that include a ... lubricant....”).

Additionally, a POSA would have found it obvious to include a particular species of lubricant in the tablet formulation. For example, Brown specifically identifies “magnesium stearate and the like” as examples of lubricants to include in its solid dosage form. Ex. 1003 at [0082]; Ex. 1007 ¶194. Remington further teaches that “[c]ommonly used lubricants include talc, *magnesium stearate*, calcium stearate, *stearic acid*, glyceryl behenate, hydrogenated vegetable oils, and polyethylene glycol (PEG).” Ex. 1004 at 892; Ex. 1025 at 697 (“Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant.”); Ex. 1007 ¶194. Thus, a POSA would have been motivated to include a widely and commonly used lubricant such as magnesium stearate or stearic acid in the tablet composition. Ex. 1007 ¶¶194-195; *see also* section II.B.4, *supra*.

A POSA would have had a reasonable expectation of successfully utilizing one or more “lubricants” such as magnesium stearate or stearic acid in view of Brown’s and Remington’s express teachings. Ex. 1007 ¶196; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise given its reliance on “known” methods/techniques in both Brown and the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

g. Tablet/Capsule

Claim 1 further requires that “the pharmaceutical composition is a tablet or capsule.” Tablets and capsules are the two most common oral dosage forms. Ex. 1004 at 889 (“Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules.”); Ex. 1007 ¶¶198-199; *see also* Section II.B, *supra*. Indeed, Brown teaches that “[s]olid dosage forms for oral administration, which includes ... tablets ... are particularly preferred.” Ex. 1003 at [0087]; Ex. 1007 ¶199.

A POSA would have been motivated to prepare a tablet. Ex. 1007 ¶199. Remington explains that “[t]ablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration).” Ex. 1004 at 889; Ex. 1007 ¶199; *see also* Section II.B,

supra. Moreover, Exelixis previously agreed that a POSA would be so motivated. Ex. 1026 at 54; *see also id.* at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule....”).

A POSA would have had a reasonable expectation of successfully preparing a tablet given Brown’s express teaching to use “known” techniques to formulate cabozantinib (L)-malate. Ex. 1003 at [0051]-[0054]; Ex. 1007 ¶200; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise given its same reliance on “known” methods/techniques in the ’349 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:38-52.

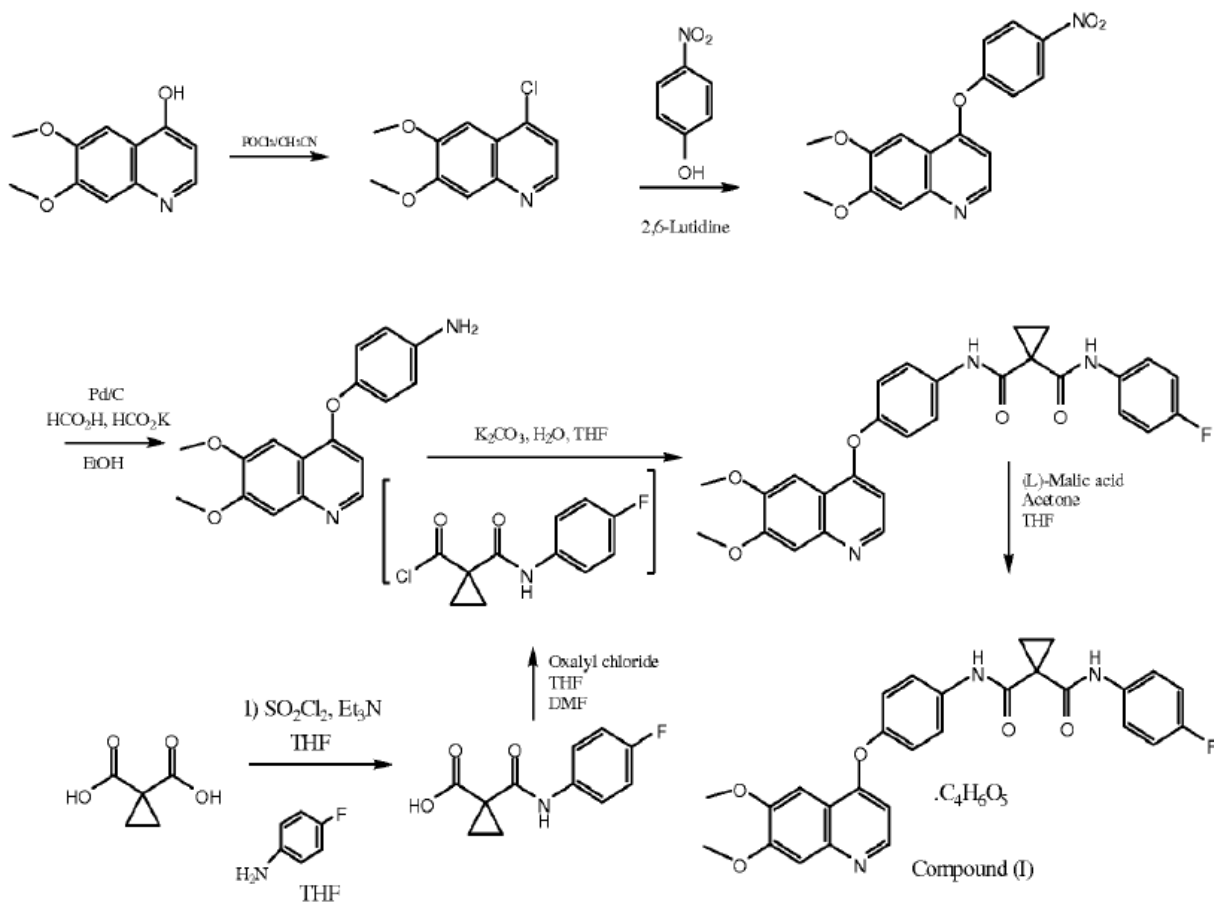
h. Achieving “Essentially Free” Levels of “Process Byproducts and Contaminants” Would Have Been Obvious

Thus far, there has been no distinction between the prior art and the Challenged Claims. While claim 1 of the ’349 patent further requires that the composition be “essentially free of process byproducts or contaminants,” the only “byproduct” or “contaminant” ever named in the ’349 patent is “6,7-dimethoxy-quinoline-4-ol.” Ex. 1001 at 22:24-27, claim 2. However, it would have been obvious to obtain a tablet or capsule composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

i. Cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol would have been obvious

Brown describes how to prepare cabozantinib (L)-malate (labeled as “Compound (I)” in Scheme 1):

SCHEME 1



Ex. 1003 at [0099]; Ex. 1027 ¶¶41. Brown’s process utilizes 6,7-dimethoxy-quinoline-4-ol as a starting material. Ex. 1003 at [0099], [00100]-[00102]; Ex. 1027 ¶¶52-53. Brown indicates that 6,7-dimethoxy-quinoline-4-ol can remain as a “reaction impurity,” whose presence in cabozantinib (L)-malate “may be determined

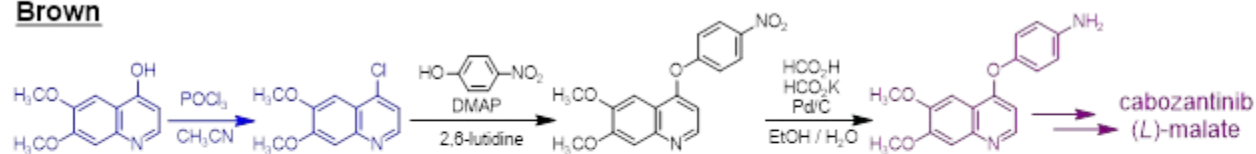
by analytical techniques known in the art.” Ex. 1003 at [00102] and [0097]; Ex. 1027 ¶54.

A POSA would have understood that Brown’s 6,7-dimethoxy-quinoline-4-ol starting material, which is the same “byproduct” or “contaminant” identified in the ’349 patent, may be present as a reaction impurity in Brown’s cabozantinib (L)-malate. Ex. 1027 ¶¶54-56, 79. Indeed, Brown’s cabozantinib (L)-malate contained “at most, de minimis” 6,7-dimethoxy-quinoline-4-ol (indicated in the upper left-hand corner of Scheme 1, *supra*). Ex. 1026 at 46 (“[A] POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process.”); *id.* at 52-53. Exelixis cannot contend otherwise. Ex. 1024 at 668:11-669:14 (Exelixis expert referring to 6,7-dimethoxy-quinoline-4-ol as the “1-1 impurity” and concluding that “a [POSA] would not believe there would be any of this material” left); Ex. 1019 at 708:23-709:19 (Exelixis expert stating “we would not expect any significant amount of [6,7-dimethoxy-quinoline-4-ol] to carry through. We just would expect it to be de minimis.”).

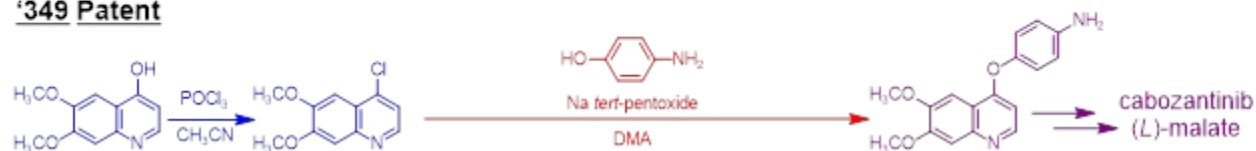
Brown’s synthesis of cabozantinib (L)-malate and the ’349 patent’s synthesis of the same material are very similar, as illustrated in Figure 1:

Figure 1—Comparison of synthetic routes in Brown and the ’349 patent

Brown

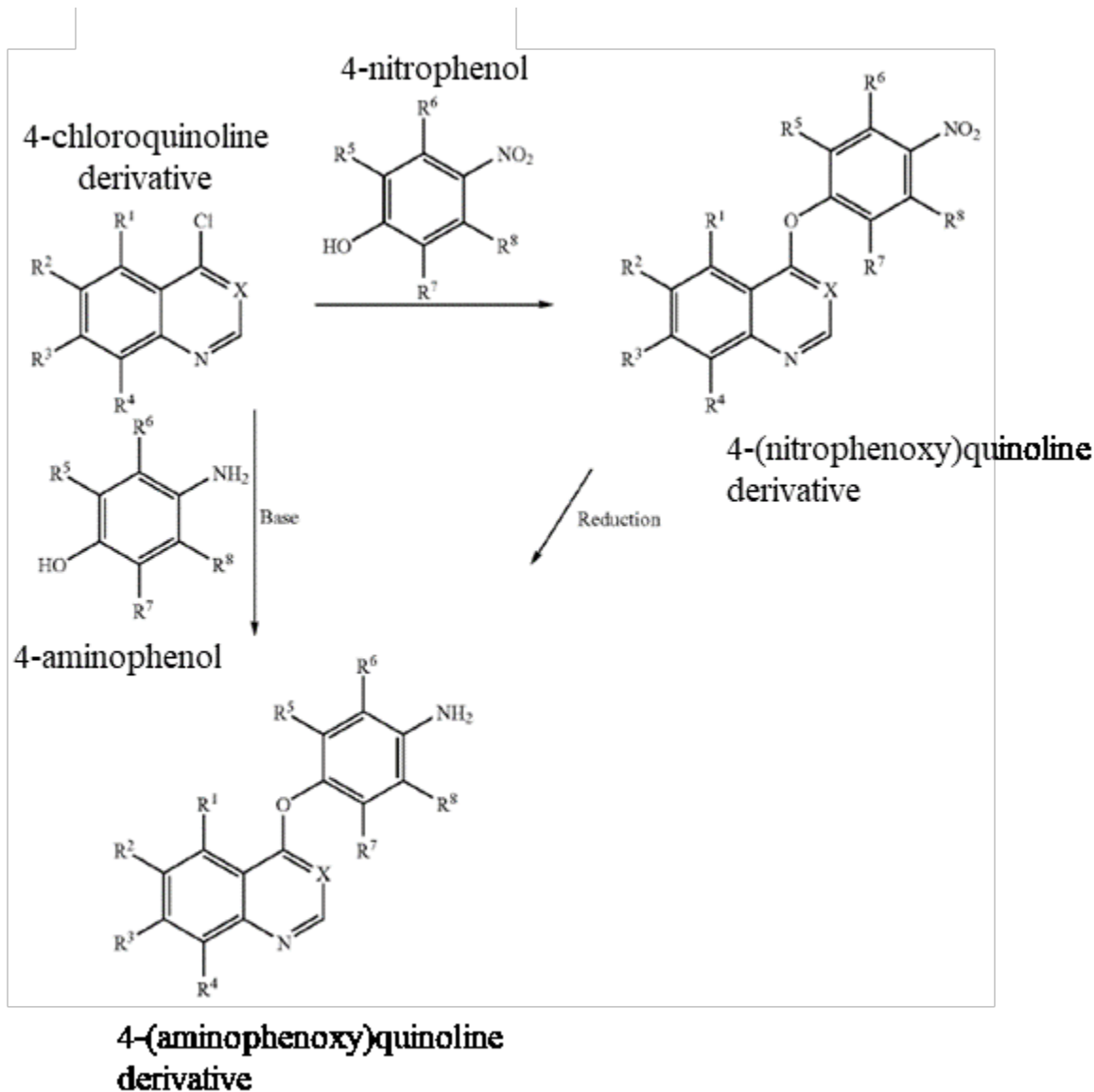


'349 Patent



Ex. 1027 ¶¶49. In Figure 1, the steps in **blue** are identical between Brown and the '349 patent's own Figure 1. Ex. 1001 at columns 23-26; Ex. 1027 ¶¶49-52. Both Brown and the '349 patent also converge to the same 4-(aminophenoxy)quinoline derivative (shown in **purple** in Figure 1), which is then subjected to the same chemical transformations to afford cabozantinib (L)-malate. Ex. 1027 ¶50. Indeed, the similarities are so strong with respect to these transformations that the only procedures identified in the '349 patent for obtaining cabozantinib (L)-malate as the crystalline N-1 or N-2 form are copied verbatim from Brown. *Compare* Ex. 1003 at [00115]-[00127] *with* Ex. 1001 at 29:40-30:60; Ex. 1027 ¶51. Thus, the sole, transformative distinction between Brown's synthesis of cabozantinib (L)-malate containing a "de minimis" amount of 6,7-dimethoxy-quinoline-4-ol and that of the '349 patent are the two steps noted in black from Brown versus the one step noted in red from the '349 patent (*see* Figure 1, *supra*). Ex. 1027 ¶¶49-52. This distinction would have been obvious.

Kubo teaches that the two steps of Brown (indicated in **black** in Figure 1, *supra*) can “[a]lternatively” be performed in a single step using 4-aminophenol. Ex. 1028 at 12:46-14:4; Ex. 1027 ¶¶60-64. This is illustrated in Kubo’s Scheme 1:



Ex. 1028 at 12:46-14:4 (Annotated); Ex. 1027 ¶¶60.

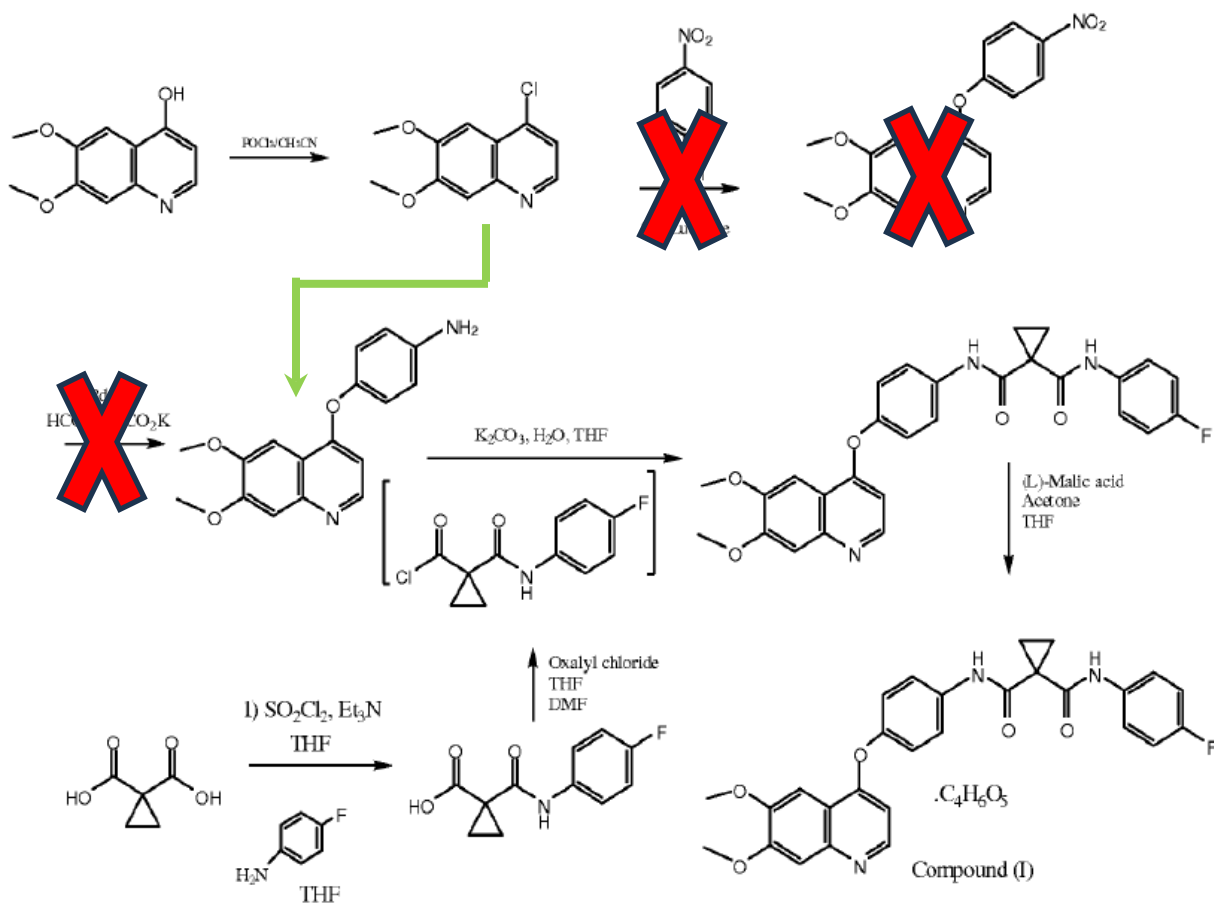
There is no question as to the relevance of Kubo’s teachings to Brown’s synthesis. Ex. 1027 ¶¶60-62. Kubo uses the same type of starting material as Brown

(a “4-chloroquinoline derivative”); Kubo uses the same type of reagents (“4-nitrophenol” and “4-aminophenol”); Kubo forms the same products (a “4-(nitrophenoxy)quinoline derivative” and a “4-(aminophenoxy)quinoline derivative”); and Kubo discusses the separation of “4-(aminophenoxy)quinoline derivative” from the same 4-hydroxyquinoline decomposition products formed in Brown. Ex. 1028 at 12:46-14:4; Ex. 1027 ¶¶62, 73-74. In sum, Kubo involves the same synthetic chemistry as Brown. Ex. 1027 ¶¶60-64. Because a POSA “has good reasons to pursue the known options within his or her technical grasp,” utilizing Kubo’s alternative, one-step approach would have been obvious. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417, 421 (2007); *see also ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) (explaining that where an “ordinary artisan would ... be left with two design choices ... [e]ach of these two design choices is an obvious combination”); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010).

Moreover, a POSA would have been motivated to apply Kubo’s one-step alternative to Brown’s preparation of cabozantinib (L)-malate. Ex. 1027 ¶¶65-74. The single-step approach saves one step in Brown’s synthesis of cabozantinib (L)-malate. Ex. 1027 ¶¶57-60, 66. For this reason alone, a POSA would have found the single-step alternative “superior.” Ex. 1029 at 133 (“A synthesis that reaches the target in fewer steps than another one is considered superior.”); Ex. 1027 ¶67.

The rationale for eliminating a step is straightforward—doing so improves efficiency. Ex. 1030 at 3012 (“[M]inimising the number of steps leads to an efficient multistep synthesis in terms of cost and time expended to obtain the desired product.”); Ex. 1031 at 2855 (“Minimizing the total number of steps ... lays a foundation for achieving overall efficiency.”); Ex. 1027 ¶67. Here, Brown’s two-step approach is neither efficient nor economical when compared to Kubo’s alternative one-step approach to make the same material that Brown must prepare. Ex. 1027 ¶67. The gain in efficiency from Kubo is further illustrated below:

SCHEME 1



Ex. 1027 ¶¶57-58, 68. Kubo's alternative use of 4-aminophenol saves money by eliminating unnecessary chemical usage and waste disposal from the unnecessary reaction. Ex. 1027 ¶69. It saves manpower by eliminating performance of the unnecessary reaction. Ex. 1027 ¶69. It eliminates a hazardous reagent. Ex. 1035 at 124440; Ex. 1027 ¶69. It saves in material costs because Brown's two-step approach resulted in a 28% yield of the 4-(aminophenoxy)quinoline derivative while it was known that the one-step approach can afford the same compound in as much as a 92% yield. Ex. 1003 at [00103]-[00106]; Ex. 1001 at 25:55-26:35; Ex. 1033 at 2186 (Scheme 1), 2190; Ex. 1027 ¶¶70-72. Kubo also teaches that the one-step approach can simplify product isolation and improve purity. Ex. 1028 at 12:60-14:2; Ex. 1027 ¶¶73-74. Thus, a POSA would have been motivated to incorporate Kubo's one-step "alternative" in Brown's preparation of cabozantinib (L)-malate for such obvious benefits. Ex. 1027 ¶¶73-74. Given the preparation of highly similar quinoline derivatives, for treating the same diseases, and using the same synthetic approach, a POSA interested in preparing cabozantinib (L)-malate would have been well aware of Kubo. Ex. 1027 ¶¶42-43, 60-64. Exelixis cannot contend otherwise—Kubo is cited on the face of the '349 patent. Ex-1001 at (56).

A POSA would have also had a reasonable expectation that applying the one-step approach taught by Kubo to Brown's synthesis of cabozantinib (L)-malate would be successful. Ex. 1027 ¶75. The one-step approach affords the same

intermediate that Brown prepared over two steps and subsequently used to prepare cabozantinib (L)-malate. *Id.* Moreover, the '349 patent is itself evidence that this one-step approach would be successful. Ex. 1001 at 10:65-12:41 (discussing “[n]on-limiting examples of suitable reaction conditions” for the one-step sequence), 17:32-18:21 (disclosing the same 2,6-lutidine base used in Brown’s Scheme for the one-step sequence), 33:44-49 (stating “many variations and modifications can be made while remaining within the spirit and scope of the invention”); Ex. 1027 ¶¶80-82.

With respect to the amount of any 6,7-dimethoxy-quinoline-4-ol impurity in cabozantinib (L)-malate, Brown’s original synthesis afforded material containing a “de minimis” amount of 6,7-dimethoxy-quinoline-4-ol. Ex. 1026 at 46, 52-53; Ex. 1024 at 668:11-669:14; Ex. 1019 at 708:23-709:19. Applying Kubo’s one-step approach to Brown’s synthesis of cabozantinib (L)-malate would have been expected to confer an additional benefit of further reducing any amount of 6,7-dimethoxy-quinoline-4-ol in the cabozantinib (L)-malate obtained from the synthesis. Ex. 1027 ¶¶76-82. Kubo expressly indicates that the one-step approach can be performed under conditions that will separate any 6,7-dimethoxy-quinoline-4-ol from the 4-(aminophenoxy)quinoline intermediate. Ex. 1028 at 12:60-14:2; Ex. 1027 ¶79.

Additionally, both the 4-(nitrophenoxy)quinoline intermediate in Brown’s synthesis and the 4-(aminophenoxy)quinoline intermediate in the one-step sequence

of Brown and Kubo are susceptible to small amounts of degradation by water to afford 6,7-dimethoxy-quinoline-4-ol. Ex. 1027 ¶¶77-78; *see also* Ex. 1024 at 600:10-601:4. However, the 4-(aminophenoxy)quinoline intermediate is less susceptible to such a degradation reaction than the 4-(nitrophenoxy)quinoline intermediate because the liberation of 4-aminophenol is less likely to occur than the liberation of 4-nitrophenol due to the difference in their stability. Ex. 1032 at 820; Ex. 1027 ¶78. By applying Kubo’s one-step approach with 4-aminophenol to Brown’s synthesis of cabozantinib (L)-malate, a POSA would have expected lower amounts of 6,7-dimethoxy-quinoline-4-ol to be present as a result of the difference in hydrolytic stability. Ex. 1027 ¶78. As a result, cabozantinib (L)-malate containing a “de minimis” amount of 6,7-dimethoxy-quinoline-4-ol as originally produced by Brown would have been expected to contain even lower amounts of 6,7-dimethoxy-quinoline-4-ol as a result of the change in synthetic process to utilize Kubo’s one-step approach. Ex. 1027 ¶79.

Moreover, Kubo’s one-step approach combined with Brown must have necessarily afforded cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Ex. 1024 at 694:13-24 (Exelixis expert testifying that the one step sequence controlled for the formation of 6,7-dimethoxy-quinoline-4-ol); Ex. 1019 at 712:1-5 (Exelixis expert testifying that “the first key difference [between Brown and the ’349 patent] is that the ’349 patent has a different synthetic process

which was designed to minimize the [6,7-dimethoxy-quinoline-4-ol] impurity at very low levels”); Ex. 1027 ¶¶80. As previously indicated, the one-step approach is the only difference between Brown’s approach to cabozantinib (L)-malate and the ’349 patent’s approach. *MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) (“MEHL/Biophile does not dispute on appeal that the laser operating parameters disclosed in the article substantially coincide with those disclosed in the patent. Accordingly, to the extent the embodiment in the patent achieves hair depilation, so does the Polla method.”); Ex. 1019 at 712:1-5; Ex. 1027 ¶¶59, 80. Thus, applying the one-step approach of Kubo must necessarily result in cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Ex. 1027 ¶¶80.

Indeed, nothing in the ’349 patent instructs a POSA as to what must actually be done to obtain cabozantinib (L)-malate containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Ex. 1027 ¶¶81-82. There is no measurement of pre-formulated API for levels 6,7-dimethoxy-quinoline-4-ol. Ex. 1027 ¶¶82. There is no discussion of what conditions do or do not result in the formation of 6,7-dimethoxy-quinoline-4-ol. Ex. 1027 ¶81. The ’349 patent simply leaves it to a POSA to figure out on its own what variables afford API having 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Even then, the ’349 patent only contains “non-limiting examples” while proclaiming that “many variations and modifications can

be made.” Ex. 1001 at 7:24-27, 8:21-24, 9:28-49, 0:65-12:41, 12:58-13:14, 24:13-28, 33:44-49; Ex. 1027 ¶81.

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. *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010) (“[T]he prior art need only meet the inherently disclosed limitation to the extent the patented method does.”). For Exelixis to contend otherwise, it must contravene its own broadly worded disclosure and read limitations into the claims.

ii. A pharmaceutical composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol would have been obvious

Section VII.D.h.i, *supra*, explained why cabozantinib (L)-malate containing less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol would have been obvious. Formulating such material into a tablet containing “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” that contained less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol would have also been obvious. Ex. 1007 ¶¶202-210. This conclusion is fully supported by the district court’s findings from the prior litigation. Ex. 1026 at 47 (“A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that include a filler, lubricant, disintegrant, and glidant.”); *id.* (“It was not unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the [6,7-dimethoxy-

quinoline-4-ol] impurity. A POSA would have expected that cabozantinib (L)-malate that is essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity could be formulated into a capsule or tablet that is essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity.”). It is a conclusion that Exelixis did not dispute. *Id.* at 54.

Exelixis cannot now contend otherwise. Its litigation expert admitted that there is nothing in the '349 patent other than the synthetic process for cabozantinib (L)-malate that would control the amount of 6,7-dimethoxy-quinoline-4-ol in the resulting pharmaceutical composition. Ex. 1019 at 773:7-24. The '349 patent admits that preparing the dosage form requires nothing more than “known techniques.” Ex. 1001 at 20:40-52, 30:65-67; Ex. 1007 ¶209. Brown teaches the same. Ex. 1003 at [0082]; Ex. 1007 ¶209. Thus, if the cabozantinib (L)-malate contains less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol before formulation as a capsule or tablet, and only “known techniques” are required to prepare a capsule/tablet, then nothing more is needed to establish obviousness. *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (“It is long settled that in the context of obviousness, the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.”) (internal quotation marks omitted); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368,

1376 (Fed. Cir. 2001). “To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.” *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

Moreover, a POSA would have been motivated to prepare a composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol due to the chemical structure of this impurity. Ex. 1007 ¶¶204-206. Quinoline was known to be genotoxic. Ex. 1036 at 11-13; Ex. 1007 ¶204. Similarly, a POSA would have known that a quinoline-containing compound such as 6,7-dimethoxy-quinoline-4-ol is potentially genotoxic. *Id.*; Ex. 1019 at 769:5-770:4 (Exelixis expert admitting that the quinoline structure of 6,7-dimethoxy-quinoline-4-ol requires further evaluation for genotoxicity). As such, a POSA would have heeded regulatory guidance regarding the identification and treatment of potentially genotoxic impurities such as 6,7-dimethoxy-quinoline-4-ol. Ex. 1007 ¶¶204-206. Such guidance requires identifying and evaluating starting materials, anticipated reaction products, and/or impurities with known or suspected genotoxic or carcinogenic potential. Ex. 1037 at 1; Ex. 1007 ¶205. Because 6,7-dimethoxy-quinoline-4-ol is both a starting material and a potential impurity in cabozantinib (L)-malate, 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. Ex. 1007 ¶¶204-206; Ex. 1019 at 769:5-770:4.

Regulatory guidance teaches that the level of a genotoxic impurity should range from less than 120 µg/day to less than 1.5 µg/day depending upon duration of treatment. Ex. 1037 at 7, 11 (Table 1); Ex. 1038 at 6-7; Ex. 1007 ¶206. A POSA would have known from the initial disclosure of cabozantinib that the amount of API intended to be administered was “about 0.1 to about 1,000 mg per day.” Ex. 1008 at 274:52-57; Ex. 1007 ¶206. Thus, a POSA could determine the suggested limit of 6,7-dimethoxy-quinoline-4-ol according to regulatory guidance. Ex. 1007 ¶206. For the range of 0.1 mg to 1000 mg per day, the limit for genotoxic impurities would have been less than 120 ppm to as low as less than 1.5 ppm. *See* Ex. 1038 at 7 (Eq. 1) (substituting 1000 mg or 1 g as the dose and either 120 µg/day or 1.5 µg/day as the Threshold of Toxicological Concern); Ex. 1007 ¶206. Accordingly, it would have been *prima facie* obvious to minimize the amount of 6,7-dimethoxy-quinoline-4-ol to less than 200 ppm per regulatory guidance. *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003). Regulatory guidance specifically identified such a limit as an acceptable measure to combat potentially genotoxic impurities. Ex. 1037 (FDA Guidance) at 12 (Table 2); Ex. 1007 ¶¶205-206.

Furthermore, Section VII.D.1.c-f, *supra*, explained why each of excipient categories and individual excipients chosen by Exelixis for use in the composition reported in Table 3 would have been obvious choices. The '349 patent later confirmed that these obvious excipients could be used to prepare a capsule

composition having 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Ex. 1001 at Table 7A-7B; Ex. 1007 ¶208. This was not unexpected, *see* Ex. 1026 at 47, particularly when such popular, commonly used excipients were combined with cabozantinib (L)-malate—an inherently “very, very, very, stable compound.” Ex. 1024 at 661:9-663:11 (Exelixis’s expert testifying to stability); Ex. 1007 ¶209. Accordingly, such a composition having the claimed impurity limitation would have been obvious as demonstrated by the ’349 patent’s own data. *MEHL*, 192 F.3d at 1366.

Thus, a POSA would have had ample motivation and expectation of success to have utilized the express teachings of Brown, Kubo, and Remington to prepare a tablet for oral administration that included “Compound IB” (cabozantinib (L)-malate) containing less than 200 ppm “6,7-dimethoxy-quinoline-4-ol” along with the broadly claimed categories of “one or more fillers” (and specifically microcrystalline cellulose), “one or more disintegrants” (and specifically croscarmellose sodium), “one or more glidants” (and specifically colloidal silica), and “one or more lubricants” (and specifically magnesium stearate or stearic acid). As such the claim 1 would have been obvious.

2. Claim 2

Claim 2 depends from claim 1 and requires that “the process byproduct or contaminant is 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition.” Ex. 1001 at claim 2; Ex. 1007 ¶213. For the reasons discussed above with respect to claim 1, claim 2 would have been obvious. *See* Sections VII.D.1, *supra*; Ex. 1007 ¶214.

3. Claim 3

The only linguistic difference between the Challenged Claims is that independent claim 3 recites that the composition is “essentially free of 6,7-dimethoxy-quinoline-4-ol” rather than “essentially free of process byproducts or contaminants” (claim 1) or “6,7-dimethoxy-quinoline-4-ol” (claim 2). Ex. 1001 at claims 1-3; Ex. 1007 ¶215. For the reasons discussed above with respect to claims 1 and 2, Brown in view of Kubo and Remington also renders claim 3 obvious. *See* Sections VII.D.1-2, *supra*; Ex. 1007 ¶¶216-226.

VIII. SECONDARY CONSIDERATIONS

Exelixis previously argued evidence of three secondary considerations of nonobviousness: commercial success, long-felt but unmet need, and unexpected results. Ex. 1026 at 56. The district court rejected Exelixis’s arguments concerning long-felt but unmet need and unexpected results. *Id.* at 57. It further found that a blocking patent diminished the strength of commercial success as an indicia of

nonobviousness. *Id.* Accordingly, Azurity is not presently aware of any allegations that would support a conclusion of nonobviousness. *See Leapfrog v. Fisher-Price*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding that “substantial evidence of commercial success, praise, and long-felt need” was inadequate “given the strength of the prima facie obviousness showing”).

IX. INSTITUTION IS WARRANTED

This petition should not be subject to discretionary denial under the Board’s §314(a) or §325(d) tests.

A. The *Fintiv* Factors do not Favor Denial

In certain circumstances that are not applicable here, the PTAB has exercised its discretion and not instituted an otherwise justified IPR where a parallel federal court litigation was addressing the same issues. 35 U.S.C. § 314(a); *Apple, Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5-6 (PTAB Mar. 20, 2020).

As discussed below in further detail, that discretion should not be exercised here. The federal court litigation that was recently decided at the trial level did not involve Petitioner here and involved different grounds of invalidity from those raised here. There was no argument about anticipation, and the obviousness argument that was tried involved different prior art.

For these and other reasons, this IPR should not be denied based upon the existence of that litigation.

1. *Fintiv* Factor 1 Disfavors Denial

There is currently no pending litigation between Exelixis and Azurity. Therefore, there is no opportunity for any stay. Accordingly, Factor 1 disfavors discretionary denial because it is presently inapplicable.

Even if, hypothetically, Exelixis did sue Azurity in the future, the District Court in that case would be unlikely to issue a stay. This is because Exelixis would almost certainly assert additional patents against Azurity—just as it has done in numerous other litigations concerning cabozantinib. Thus, the District Court will have no reason to stay proceedings in view of this IPR proceeding. Accordingly, under this hypothetical scenario, Factor 1 would be neutral.

2. *Fintiv* Factor 2 Disfavors Denial

The Board's projected statutory deadline for a final written decision is approximately 18 months from the filing of this petition. There is currently no parallel proceeding between Exelixis and Azurity in a district court. Thus, the Board's projected statutory deadline should be well-before any future district court's trial date. Accordingly, Factor 2 disfavors discretionary denial.

3. *Fintiv* Factors 3 and 4 Disfavor Denial

There is no parallel proceeding between Azurity and Exelixis in a district court. Accordingly, neither party nor a district court has invested any resources. Thus, Factors 3 and 4 should disfavor denial.

Assuming, *arguendo*, that the Board were to consider the district court proceeding between MSN and Exelixis as a “parallel proceeding” for the purposes of evaluating the *Fintiv* Factors, discretionary denial would still be disfavored. There are several differences between this petition’s arguments and those tried between MSN and Exelixis in district court. First, only claim 3 was at issue in the MSN/Exelixis litigation. This petition, however, challenges every claim of the ’349 patent. Second, in the pending litigation, the effective filing date of the ’349 patent’s claims was never considered. Thus, there is no overlap between this petition’s Ground 1 and the MSN/Exelixis litigation. Lastly, the petition’s Ground 2 relies upon a secondary reference (“Kubo”) that, when combined with Brown, explains why it would have been obvious to obtain cabozantinib (L)-malate containing 200 ppm or less of a potentially genotoxic impurity, 6,7-dimethoxy-quinoline-4-ol, particularly in view of regulatory guidance. Ground 2 then explains why, with such material in hand, the pharmaceutical composition recited in the Challenged Claims would have been obvious as well as why each of the individual excipient species utilized in the ’349 patent’s working examples would have been obvious. Such arguments were not presented in the MSN/Exelixis litigation.

Accordingly, any overlap between this petition and the MSN/Exelixis litigation is either a consequence of Exelixis’s admissions or the closeness of the prior art. Thus, Factors 3 and 4 disfavor discretionary denial.

4. *Fintiv* Factor 5 Disfavors Denial

Azurity was not a party to the MSN/Exelixis litigation. Accordingly, Factor 5 should disfavor discretionary denial. However, in *Fintiv* the Board held that: “An unrelated petitioner should [] address any other district court or Federal Circuit proceedings involving the challenged patent to discuss why addressing the same or substantially the same issues would not be duplicative of the prior case even if the petition is brought by a different party.” *Fintiv* Order at 14 (internal references omitted). Azurity explained the disparate issues between this petition and the MSN/Exelixis litigation concerning Factors 3 and 4, *supra*. Thus, Factor 5 disfavors discretionary denial.

5. *Fintiv* Factor 6 Disfavors Denial

Director Vidal issued a precedential order in *Commscope Tech. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 (PTAB Feb. 27, 2023), indicating that “[t]he Board should first assess *Fintiv* factors 1–5; if that analysis supports discretionary denial, the Board should engage the compelling merits question” that is *Fintiv* Factor 6. As indicated above, *Fintiv* Factors 1-5 disfavor discretionary denial. Accordingly, the Board need not consider *Fintiv* Factor 6. However, should the Board do so, Factor 6 also disfavors discretionary denial.

“[W]hen determining whether there is a compelling unpatentability challenge, the Board evaluates whether the Petition presents challenges ‘in which the evidence,

if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.” *Commscope*, Paper 23 at 3. That is the present situation. Exelixis’s failure to rebut the petition’s arguments concerning the effective filing date of the Challenged Claims inexplicably results in anticipation by an earlier-published family member. Thus, in view of at least Ground 1, Factor 6 disfavors discretionary denial. Moreover, when one scrutinizes the disclosure of the ’349 patent against that of Brown and Kubo and compares it against the breadth of the claims as the petition has done in Ground 2, there is no daylight left to conclude that the Challenged Claims are anything but obvious. Thus, Ground 2 also disfavor discretionary denial.

B. The *Advanced Bionics* Test Does Not Favor Denial

In determining whether to exercise discretion to deny institution under §325(d), the Board applies the *Advanced Bionics* test. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 (PTAB Feb. 13, 2020) (Paper 6) (precedential) (“(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.”).

1. *Advanced Bionics* does not apply to Ground 1

The effective filing date of the Challenged Claims was not considered during examination. Accordingly, the Office was not presented the same art or the same arguments as in Ground 1.

2. *Advanced Bionics* favors institution for Ground 2

With respect to Ground 2, 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. Applicant overcome the Examiner’s obviousness rejection by arguing that the cited art (“Brown”) did not disclose the claimed purity requirement or the incorporation of “one or more glidants.” Ex. 1014 at 82. As explained in the petition, the Examiner failed to appreciate that the combination of Brown and Kubo teaches the preparation of cabozantinib (L)-malate as broadly described in the ’349 patent. Moreover, the Examiner did not have the benefit of Exelixis’s admissions and expert’s statements regarding a motivation to formulate cabozantinib (L)-malate with each of the excipient categories recited in the Challenged Claims. Thus, the Examiner should not have acquiesced to Exelixis’s arguments regarding purity or the incorporation of a glidant.

Additionally, Petitioner’s Ground 2 utilizes a pharmaceutical treatise (“Remington”) that was not submitted to the Examiner during prosecution. This

textbook explains that not only were the categories of excipients recited in the Challenged Claims commonly included in tablet compositions, but that each of the species of excipients utilized in the '349 patent's working examples were common and popular excipients for preparing a tablet or capsule composition. For these reasons, the two-step *Advanced Bionics* test does not disfavor institution.

X. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(A)(1)

Pursuant to 37 C.F.R. §42.8(a)(1), the mandatory notices identified in 37 C.F.R. §42.8(b) are provided below as part of this Petition.

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Azurity Pharmaceuticals, Inc. is the Petitioner and real-party-in-interest. Slayback Pharma LLC is a wholly-owned subsidiary of Azurity Pharmaceuticals, Inc.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is aware of the following judicial or administrative matters that would affect, or be affected by, a decision in the proceeding:

Exelixis, Inc. v. Cipla Ltd. et al., 1-24-cv-00565 (DDE)

Exelixis, Inc. v. Cipla Ltd. et al., 1-23-cv-00287 (DDE)

Exelixis, Inc. v. Teva Pharmaceutical Industries Ltd. et al., 1-22-cv-01168 (DDE)

Exelixis, Inc. v. MSN Laboratories Private Limited et al., 1-22-cv-00945
(DDE)

Petitioner is aware of the following patents and patent applications related to the '349 patent: U.S. 9,717,720; U.S. 10,123,999; U.S. 10,543,206; U.S. Application Serial No. 16/706,323; U.S. Application Serial No. 17/152,394; U.S. Application Serial No. 17/497,201; U.S. Application Serial No. 17/957,505; U.S. Application Serial No. 18/462,739; U.S. Application Serial No. 17/679,634; U.S. 12,128,039; U.S. Application Serial No. 18/899,774.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Azurity provides the following designation of counsel, all of whom are identified in Azurity's Power of Attorney.

Lead Counsel	Back-up Counsel
Andrew E. Morrell (Reg. No. 63,747) amorrell@windelsmarx.com WINDELS MARX LANE & MITTENDORF, LLP One Giralda Farms Madison, NJ 07940 Tel.: 973-966-3200	Ajay Kayal (Reg. No. 66,691) akayal@windelsmarx.com Leah Digby (Reg. No. 82,956) lkuhn@windelsmarx.com WINDELS MARX LANE & MITTENDORF, LLP One Giralda Farms Madison, NJ 07940 Tel.: 973-966-3200

D. Service Information (37 C.F.R. §42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the addresses shown above. Petitioner also consents to electronic service by email to AzurityIPRs@windelsmarx.com.

XI. PAYMENT OF FEES

The undersigned authorize the Office to charge the §42.15(a) review fee to Deposit Account No. 603243. Review of 3 claims is requested. Payment of additional fees due is authorized to be charged to this Account.

XII. ADDITIONAL REQUIREMENTS UNDER 37 C.F.R. §42.104

Azurity certifies that the '349 patent is available for IPR and is not barred or estopped from requesting IPR challenging the claims on the identified grounds.

XIII. CONCLUSION

Claims 1-3 of the '349 patent are unpatentable and should be canceled.

Respectfully submitted,

WINDELS MARX LANE & MITTENDORF, LLP

Dated: November 18, 2024

By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
Ajay Kayal (Reg. No. 66,691)
Leah Digby (Reg. No. 82,956)
Jason Lief (pending *pro hac vice*)

Attorneys/Practitioners for Petitioner
Azurity Pharmaceuticals, Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 11,298,349** complies with the type-volume limitation of 37 C.F.R. §42.24(a)(1). According to Microsoft Office Word 2016’s word count, this Petition contains 13,905 words, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a).

Respectfully submitted,

WINDELS MARX LANE & MITTENDORF,
LLP

Dated: November 18, 2024

By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
Ajay Kayal (Reg. No. 66,691)
Leah Digby (Reg. No. 82,956)

Attorneys/Practitioners for Petitioner
Azurity Pharmaceuticals, Inc.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 11,298,349** and **EXHIBITS 1001-1038** are being served on November 18, 2024, via Federal Express overnight delivery at the correspondence address for U.S. 11,298,349 as identified in Patent Center:

Jonathan P. O'Brien, Ph.D./Exelixis
Honigman LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

Service is also being effected by sending a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 11,298,349** and **EXHIBITS 1001-1038**, via Federal Express overnight delivery to the address of Exelixis, Inc.:

Jeffrey J. Hessekiel, J.D.
Exelixis, Inc.
1851 Harbor Bay Parkway
Alameda, CA 94502

Dated: November 18, 2024 By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
Ajay Kayal (Reg. No. 66,691)
Leah Digby (Reg. No. 82,956)

Attorneys/Practitioners for Petitioner
Azurity Pharmaceuticals, Inc.