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

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.

Petitioner,

v.

EXELIXIS, INC.

Patent Owner.

IPR2025-00427
Patent 12,128,039

**PETITIONER'S SUR-REPLY TO PATENT OWNER'S REPLY TO
PETITIONER'S OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF**

EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent 12,128,039 (“the ’039 patent”)
1002	<i>Exhibit Number Not Used</i>
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	<i>Exhibit Number Not Used</i>
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, 22-cv-00228-RGA, D.I. 168 (D.Del.)</i>
1011	<i>Exhibit Number Not Used</i>
1012	<i>Exhibit Number Not Used</i>
1013	<i>Exelixis v. MSN, 22-cv-00228-RGA, D.I. 176 (D.Del.)</i>
1014	<i>Exhibit Number Not Used</i>
1015	<i>Exhibit Number Not Used</i>
1016	<i>Exhibit Number Not Used</i>
1017	<i>Exhibit Number Not Used</i>
1018	<i>Exelixis v. MSN, 22-cv-00228-RGA, D.I. 175 (D.Del.)</i>

Exhibit No.	Description
1019	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 163 (D.Del.)
1020	<i>Exhibit Number Not Used</i>
1021	<i>Exhibit Number Not Used</i>
1022	<i>Exhibit Number Not Used</i>
1023	<i>Exhibit Number Not Used</i>
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) (“Handbook”)
1026	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 186 (D.Del.) (“Trial Opinion”)
1027	<i>Exhibit Number Not Used</i>
1028	U.S. Patent 7,169,789 (“Kubo”)
1029	Hoffmann, “Elements of Synthesis Planning,” (2009), 133-144 (“Hoffmann”)
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 (“Burns”)
1032	Pross <i>et al.</i> , “Theoretical Approach to Substituent Effects. Phenols and Phenoxide Ions,” <i>J. Org. Chem.</i> , 45 (1980), 818-826 (“Pross”)
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 (“Furuta”)
1034	Aulton, Chapter 31 (“Dosage Form Design and Manufacture”), In <i>Aulton’s Pharmaceuticals: The Design and Manufacture of Medicines</i> , 3 rd Edition, 441-482 (“Aulton”)

Exhibit No.	Description
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 (“Felpin”)
1036	Toxicological Review of Quinoline (2001) by the U.S. Environmental Protection Agency (“EPA Tox. Review”)
1037	Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008) (“FDA Genotoxic Guidance”)
1038	European Medicines Agency, Guideline on the Limits of Genotoxic Impurities (2006) (“EMA Guidance”)
1039	Robinson, “Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective,” <i>Organic Process Research & Development</i> (2010), vol. 14, 946-59 (“Robinson”)
1040	U.S. Patent 8,067,436 (“the ’436 patent”)
1041	Guidance for Industry, Q3A Impurities in New Drug Substances (June 2008) (“FDA Q3A”)
1042	Declaration of Graham Buckton, Ph.D.
1043	Declaration of William Dichtel, Ph.D.
1044	Declaration of Robert Dreicer, M.D.
1045	Prosecution History excerpt for U.S. Application Serial No. 18/436,836, which issued as the ’039 patent (Ex. 1001)
1046	U.S. Patent 11,298,349 (“the ’349 patent”)
1047	U.S. Patent 8,877,776 (“the ’776 patent”)
1048	U.S. Patent 11,098,015 (“the ’015 patent”)

Exhibit No.	Description
1049	Maddula <i>et al.</i> , “Preparative Chromatography Technique in the Removal of Isostructural Genotoxic Impurity in Rizatriptan: Use of Physicochemical Descriptors of Solute and Adsorbent,” <i>Organic Process Research & Development</i> (2009), vol. 13, 683-89 (“Maddula”)
1050	<i>Exhibit Number Not Used</i>
1051	U.S Patent Publication No 2009/0105299 (“the ’299 publication”)
1052	Guidance for Industry, Q3B(R2) Impurities in New Drug Products (August 2006) (“FDA Q3B”)
1053	“Bristol-Myers Squibb and Exelixis collaborate on kinase inhibitors,” <i>Nature Reviews Drug Discovery</i> , Volume 8, February 2009, page 1 (“BMS Collaboration”)
1054	Prosecution History excerpt for U.S. Application Serial No. 11/753,514, which issued as the ’436 patent (Ex. 1040)
1055	Huynh, “Molecularly targeted therapy in hepatocellular carcinoma,” <i>Biochemical Pharmacology</i> , vol. 80 (2010), 550-560 (“Huynh”)
1056	Guiochon, “Preparative liquid chromatography,” <i>Journal of Chromatography A</i> , 965 (2002), 129-161 (“Guiochon”)
1057	Ratain <i>et al.</i> , “Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients with Metastatic Renal Cell Carcinoma,” <i>J. Clin. Oncol.</i> , vol. 24 (2006), 2505-2512 (“Ratain”)
1058	Gotink <i>et al.</i> , “Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action?” <i>Angiogenesis</i> , vol. 13 (2010), 1-14 (“Gotink”)
1059	Sherman, “Advances in Chemotherapy of Differentiated Epithelial and Medullary Thyroid Cancers,” <i>J. Clin. Endocrinol. Metab.</i> , vol. 94(5) (May 2009), 1493-1499 (“Sherman”)

Exhibit No.	Description
1060	Salgia <i>et al.</i> , “A phase 1 dose-escalation study of the safety and pharmacokinetics (PK) of XL184, a VEGFR and MET kinase inhibitor, administered orally to patients (pts) with advanced malignancies,” <i>J. Clin. Oncol.</i> , vol. 25 (Number 18_Supplement) (2007), Abstract 14031 (“Salgia”)
1061	Van Cutsem <i>et al.</i> , “Phase 2 study of XL184 (BMS-907351) in a cohort of patients (pts) with hepatocellular carcinoma (HCC),” Thursday, November 18 (2010), Poster 408 (“Van Cutsem”)
1062	Eder <i>et al.</i> , “Novel Therapeutic Inhibitors of the c-Met Signaling Pathway in Cancer,” <i>Clin. Cancer Res.</i> , vol. 15(7) (2009), pages 2207-2214 (“Eder”)
1063	Joly, “Simultaneous blockade of VEGF and HGF receptors results in potent anti-angiogenic and anti-tumor effects,” Wednesday, November 8 (2010), Poster 104 (“Joly”)
1064	Hutson <i>et al.</i> , “Novel Therapeutics for Metastatic Renal Cell Carcinoma,” <i>Cancer</i> , May 15 (2009), pages 2361-2367 (“Hutson”)
1065	Brandt, A. and Kueppers, S., “Practical Aspects of Preparative HPLC in Pharmaceutical Development and Production,” <i>LCGC Asia Pacific</i> Volume 5, No. 2 (June 2002), 8-11 (“Brandt”)
1066	Complaint asserting the ’039 patent in <i>Exelixis, Inc. v. MSN Laboratories Private Ltd. et al.</i> , C.A. No. 1:25-cv-00346 (D. Del.)
1067	Azurity’s <i>Sotera</i> Stipulation filed in <i>Exelixis, Inc. v. Azurity Pharmaceuticals, Inc. et al.</i> , C.A. No. 1:25-cv-00478 (D. Del.)
1068	<i>Exelixis, Inc. v. MSN Laboratories Private Ltd. et al.</i> , Appeal No. 2025-1241 (Fed. Cir.) (“Notice of Docketing” dated Dec. 3, 2024)

As authorized (Ex. 3101), Azurity submits a sur-reply addressing Exelixis' arguments in response to Azurity's opposition brief ("Paper 11").

Azurity's Timely Sotera Stipulation Is Highly Relevant: Exelixis filed its Discretionary Denial Brief on May 5th—11 days after it amended its complaint for patent infringement against Azurity and the same day the waiver of service was filed. It is absurd for Exelixis to argue that Azurity "should" have filed this stipulation while the ink was still wet on the operative complaint. *See* Paper 11 at 1.

Exelixis cites no authority requiring Azurity to file its *Sotera* stipulation before Exelixis' Discretionary Denial Brief. The Board recently held that "a *Sotera* stipulation filed before the institution decision is considered timely." *Stingray Group Inc. v. Hernandez-Mondragon*, IPR2025-00350, Paper 18 at 7-8 (P.T.A.B. June 13, 2025) (citing Scott R. Boalick, Chief Administrative Patent Judge, Guidance on USPTO's rescission of "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation" (USPTO March 24, 2025) ("Guidance Memo") 2 n.1 and *NXP USA, Inc. v. Impinj, Inc.*, IPR2021-01556, Paper 13 (Sept. 7, 2022); *see also BMW of North America LLC v. Northstar Systems LLC*, IPR2023-01017, Paper 12 at 10 (P.T.A.B. Dec. 8, 2023) ("Patent Owner has not brought to our attention any binding precedent that establishes a time limit by which a *Sotera* stipulation must be submitted before we enter our decision

on institution, and we are not aware of any such precedent.”). Accordingly, Azurity’s stipulation was timely.

Azurity’s *Sotera* stipulation is also “highly relevant” to discretionary denial considerations. *See* Guidance Memo at 2-3. It mitigates “duplicative efforts between the district court and the Board, as well as concerns of potentially conflicting decisions.” *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 19 (P.T.A.B. Dec. 1, 2020). Exelixis’ argument that the stipulation does not prevent Azurity from pursuing invalidity grounds that could not be brought in an IPR illustrates its fundamental error—such grounds are not overlapping and are therefore irrelevant considerations under *Fintiv*’s fourth factor that expressly considers overlap. *See* Paper 11 at 1; *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 6 (P.T.A.B. Mar. 20, 2020) (“[O]verlap between issues raised in the petition and in the parallel proceeding”). As such, non-overlapping issues cannot be a basis for the Board to deny institution under §314.

Exelixis’ support for its argument—IPR estoppel—is also curious and inapposite to the Board’s considerations here. *See* Paper 11 at 1. IPR estoppel only applies post-institution and final written decision. 35 U.S.C. §315(e)(2). The present issue is discretionary denial in view of a *Sotera* stipulation under a different statute (§314), different precedent (*Fintiv*), and different timing (pre-institution) than IPR estoppel to address concerns regarding overlapping arguments in parallel

proceedings. Exelixis’ reliance on a future, post-institution outcome to argue for pre-institution relief makes little sense. So too is Exelixis’s speculative rationale of “parallel, duplicative challenges” filed by parties that are not under Azurity’s control somehow warrant denial of the present challenge. *See* Paper 11 at 1.

Denial In IPR2025-00210 Does Not Affect This Proceeding: Exelixis incorrectly seeks to leverage the Board’s denial in IPR2025-00210 in this proceeding (IPR2025-00427) as a referendum on the merits of different grounds. First, Exelixis’ attempt is procedurally improper. Any evaluation of merits within the framework of a discretionary denial determination is a factor that is only reached after consideration of *Fintiv* Factors 1-5. *See CommScope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 4-5 (Feb. 27, 2023). As Exelixis has to date failed to address these factors, and none warrant discretionary denial, the determination in IPR2025-00210 should not affect this proceeding under the Board’s precedential *CommScope* decision.

Moreover, Exelixis is inviting the Board to compound error on error. After arguing that the ’349 patent petition “included substantially similar arguments to those made here in Ground II,” Exelixis concedes this is not true. “[T]he ’349 patent petition did not expressly rely on Robinson[.]” Paper 11 at 2-3. Similarly, Exelixis admits that Robinson’s “exemplification of purification by chromatography” was not before the Board in IPR2025-00210. *Id.* at 3. As such, the non-cumulative and

significant discussion of Robinson, the motivation it afforded, and the expectation of success it provided in removing the claimed impurity as detailed in Ground 2 of the current proceeding was not before the Board in IPR2025-00210. *See* Paper 9 at 18-19 (citing Petition at 55-57), 31-33 (explaining why Robinson is not cumulative).

Under any definition of “novel” or “substantial similarit[y]” that Exelixis may allege, Ground 2 exceeds the definition. *See* Paper 11 at 3. That is facially evident from Exelixis’ above-noted concessions. Moreover, it is not Azurity’s job to fabricate “substantial similarities” between different petitions and different grounds and then rebut them as Exelixis suggests. *See* Paper 11 at 3. That is Exelixis’ job, and it has now twice failed its opportunities to do so. A cursory examination of the grounds of IPR2025-00210 and Ground 2 of this petition reveals the substantial differences, which renders Exelixis’ failure unremarkable.

Exelixis Misunderstands How Co-Pending Litigations Are Initiated: “A civil action is commenced by filing a complaint with the court.” Fed. R. Civ. P. 3. Azurity filed no complaint to initiate co-pending district court litigation. Thus, it is plainly evident that Exelixis initiated the co-pending litigation well-after Azurity filed its petition. Furthermore, Exelixis’ discussion of the “process” is incorrect. *See* Paper 11 at 4. The Hatch-Waxman Act afforded Exelixis the choice to initiate a civil action and obtain a benefit for choosing to do so. *See* 21 U.S.C. §355(c)(3)(C). However, the Hatch-Waxman Act did not require Exelixis to initiate

a civil action. *See id.* (“if such an action is brought”). Otherwise, there would be no reason for the Hatch-Waxman Act to afford Azurity the choice to initiate a civil action if Exelixis had not brought one. *See* 21 U.S.C. §355(c)(3)(D) (“may...bring a civil action”). Exelixis’ argument is simply incorrect according to rule and statute.

Robinson Was Not At Issue In The MSN Litigation: When the District Court found that a person of ordinary skill in the art “would heed FDA guidance on how to deal with genotoxic impurities” and “would be motivated to identify the 1-1 starting material as genotoxic,” Robinson (i.e., DTX-328) was not cited or discussed. *See* Ex. 1026, 45 (¶4) (citing trial testimony at 301:8-10, 302:4-8, 303:5-15); Ex. 2001 at 301:8-10, 302:4-8, 303:5-15 (discussing DTX-91 rather than Robinson). Moreover, the only other citation that Exelixis musters for the supposed reliance on Robinson in the District Court’s opinion is on page 53 of Ex. 1026. Here too, the opinion refers to “FDA Guidance” rather than Robinson. Exelixis’ attempts to turn the District Court proceedings into a rejection of Robinson’s disclosures is without merit. If Robinson had been “at issue,” it would have been cited in defendants’ post-trial briefing. It was not. *See* Ex. 2014. If Robinson was a critical reference “at issue” that Exelixis had to overcome, surely Exelixis would have provided it to the Patent Office for consideration. It did not. *See* Ex. 1001 (“Other Publications”).

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Respectfully submitted,

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Dated: June 19, 2025

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITIONER’S
SUR-REPLY TO PATENT OWNER’S REPLY TO PETITIONER’S
OPPOSITION TO PATENT OWNER’S DISCRETIONARY DENIAL BRIEF**
is being served on June 19, 2025, via e-mail, as consented to by Patent Owner, on
the following attorneys of record:

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