

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner

v.

CELGENE CORPORATION,
Patent Owner

Case IPR2023-00512
U.S. Patent No. 8,846,628
Issued: September 30, 2014

Title:
ORAL FORMULATIONS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

**PETITIONER'S SECOND SET OF OBJECTIONS TO
PATENT OWNER'S EVIDENCE PURSUANT TO 37 C.F.R. § 42.64**

Petitioner's Second Set of Objections to Evidence

Pursuant to 37 C.F.R. § 42.64(b)(1), Petitioner Apotex Inc. ("Petitioner") submits the following objections to evidence served by Celgene Corporation ("Patent Owner") with Patent Owner's Response ("POR") (Paper No. 15), in the above-captioned proceeding. These objections are timely under 37 C.F.R. § 42.64(b)(1) because they are being filed within five (5) business days of service of evidence to which these objections are directed. Petitioner's objections provide notice to Patent Owner that Petitioner may move to exclude these exhibits under 37 C.F.R. § 42.64(c). Petitioner's objections apply equally to Patent Owner's reliance on the exhibit in any documents concurrently-filed with the exhibit or any subsequently-filed documents.

In this paper, a reference to "FRE" means the Federal Rules of Evidence and "'628 patent" means U.S. Patent No. 8,846,628. Exhibit descriptions provided in Table 1 are from Patent Owner's exhibit list and are used for identification purposes only. The use of an exhibit description does not indicate that Petitioner agrees with that description or characterization of the document.

Notwithstanding these objections, Petitioner expressly reserves the right to rely on any evidence submitted by Patent Owner, including on the ground that such evidence constitutes a party admission.

Petitioner incorporates by reference and reiterates, as if expressly stated herein, all objections previously served on Patent Owners on August 3, 2023.

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Petitioner objects to Exhibits 2051-2054 as incomplete, lacking relevance, and because any probative value is substantially outweighed by the danger of undue prejudice (due to confusing the issues, misleading the fact finder, undue delay, wasting time, and/or needlessly presenting cumulative evidence). *See* FRE 106, 401, 402, and 403.

Petitioner further objects to Exhibit 2051, "Expert Declaration of Cory Berkland, Ph.D." Petitioner objects to ¶¶ 30-32, 34-38, 40-41, 43-45, 47, 70-85, 88-98, 100-104, 106-107, 109-115, 118-124, 126-134, 136-144, 149 of Exhibit 2051 and all paragraphs that rely on those paragraphs. These paragraphs lack a disclosed basis of sufficient facts or data (FRE 705; 37 C.F.R. § 42.65), are not based on sufficient facts or data (FRE 702), and/or are not the product of reliable principles and methods (FRE 702). Additionally, Petitioner objects to the above referenced paragraphs of Exhibit 2051 and all paragraphs that rely on those paragraphs as misleading, incomplete, and lacking relevance and because any probative value is substantially outweighed by the danger of unfair prejudice, confusing the issues, misleading the fact finder, undue delay, wasting time, and needlessly presenting cumulative evidence (FRE 106, 401, 402, and 403).

Petitioner further objects to ¶¶ 1-29, 42, 45-49, 51-60, 70-74, 94, 120, 122-126, 135, 145-146, 150-151 of Exhibit 2051 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs are irrelevant (FRE 401 and 402),

Petitioner's Second Set of Objections to Evidence and any probative value is substantially outweighed by the risk of undue prejudice and/or confusion (FRE 403).

Petitioner further objects to ¶¶ 29-31, 45, 47, 52-53, 98, 119-120, 144 of Exhibit 2051 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs rely on out of court statements for their truth, thus constituting impermissible hearsay. *See* FRE 801-804.

Petitioner further objects to Exhibit 2052, "Expert Declaration of George M. Grass IV, Ph.D." Petitioner objects to ¶¶ 26, 39-46, 48-60, 62-77, 79-87, 92-97 of Exhibit 2052 and all paragraphs that rely on those paragraphs. These paragraphs lack a disclosed basis of sufficient facts or data (FRE 705; 37 C.F.R. § 42.65), are not based on sufficient facts or data (FRE 702), and/or are not the product of reliable principles and methods (FRE 702). Additionally, Petitioner objects to the above referenced paragraphs of Exhibit 2052 and all paragraphs that rely on those paragraphs as misleading, incomplete, and lacking relevance and because any probative value is substantially outweighed by the danger of unfair prejudice, confusing the issues, misleading the fact finder, undue delay, wasting time, and needlessly presenting cumulative evidence (FRE 106, 401, 402, and 403).

Petitioner further objects to ¶¶ 1-15, 25-26, 31-34, 36-38, 91-92, 96, 99-100 of Exhibit 2052 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs are irrelevant (FRE 401 and 402), and any probative value is

Petitioner's Second Set of Objections to Evidence substantially outweighed by the risk of undue prejudice and/or confusion (FRE 403).

Petitioner further objects to ¶¶ 15, 26, 92, 96-97 of Exhibit 2052 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs rely on out of court statements for their truth, thus constituting impermissible hearsay. *See* FRE 801-804.

Petitioner further objects to Exhibit 2053, "Expert Declaration of William G. Blum, MD." Petitioner objects to ¶¶ 21, 24-40, 47 of Exhibit 2053 and all paragraphs that rely on those paragraphs. These paragraphs lack a disclosed basis of sufficient facts or data (FRE 705; 37 C.F.R. § 42.65), are not based on sufficient facts or data (FRE 702), and/or are not the product of reliable principles and methods (FRE 702). Additionally, Petitioner objects to the above referenced paragraphs of Exhibit 2053 and all paragraphs that rely on those paragraphs as misleading, incomplete, and lacking relevance and because any probative value is substantially outweighed by the danger of unfair prejudice, confusing the issues, misleading the fact finder, undue delay, wasting time, and needlessly presenting cumulative evidence (FRE 106, 401, 402, and 403).

Petitioner further objects to ¶¶ 1-10, 17-23, 28, 38-40, 48-50 of Exhibit 2053 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs are irrelevant (FRE 401 and 402), and any probative value is

Petitioner's Second Set of Objections to Evidence substantially outweighed by the risk of undue prejudice and/or confusion (FRE 403).

Petitioner further objects to ¶¶ 21, 32-47 of Exhibit 2053 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs rely on out of court statements for their truth, thus constituting impermissible hearsay. *See* FRE 801-804.

Petitioner further objects to Exhibit 2054, "Expert Declaration of Jeffrey Etter, Ph.D." Petitioner objects to the entirety of Exhibit 2054 (1) as an improper expert declaration by an interested fact witness and (2) as irrelevant and unduly prejudicial because it contains opinions and/or factual recitations not based on patents or printed publications. FRE 401-403; *see also* 35 U.S.C. § 311(b), Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019) at 36 ("expert testimony may explain 'patents and printed publications,' but is not a substitute for disclosure in a prior art reference itself.")

Petitioner further objects to ¶¶ 8-35 of Exhibit 2054 and all paragraphs that rely on those paragraphs. These paragraphs lack a disclosed basis of sufficient facts or data (FRE 705; 37 C.F.R. § 42.65; FRE 403), are not based on sufficient facts or data, are not the product of reliable principles and methods (FRE 702; FRE 403), are not based on the kinds of facts or data experts would reasonably rely on in forming an opinion (FRE 703), and/or are based on facts or data that would

Petitioner's Second Set of Objections to Evidence otherwise be inadmissible and the probative value of these paragraphs do not outweigh their prejudicial effect (FRE 703; FRE 705; 37 C.F.R. § 42.63). Additionally, Petitioner objects to the above referenced paragraphs of Exhibit 2054 and all paragraphs that rely on those paragraphs as misleading, incomplete, and lacking relevance and because any probative value is substantially outweighed by the danger of unfair prejudice, confusing the issues, misleading the fact finder, undue delay, wasting time, and needlessly presenting cumulative evidence. *See* FRE 106, 401, 402, and 403.

Petitioner further objects to ¶¶ 8-35 of Exhibit 2054 for a lack of evidence sufficient to support a finding that the witness has personal knowledge of the matter (FRE 602) and/or as improper lay testimony (FRE 701).

Petitioner further objects to ¶¶ 1, 3-7, 36-38 of Exhibit 2054 and all paragraphs that rely on those paragraphs. These paragraphs are irrelevant (FRE 401 and 402), and any probative value is substantially outweighed by the risk of undue prejudice and/or confusion (FRE 403).

Petitioner further objects to ¶¶ 12, 35 of Exhibit 2054 and all paragraphs of any declaration that rely on those paragraphs. These paragraphs rely on out of court statements for their truth, thus constituting impermissible hearsay. *See* FRE 801-804.

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Petitioner also objects to Exhibits 2051-2054 for lacking relevance to the extent they rely on or cite to a document with a purported date that is after the priority date of the '628 patent for any purpose other than in connection with a purported unexpected results, industry praise, skepticism, or satisfaction of a long-felt need (but not the existence of a long-felt need). *See* FRE 401, 402, and 403. Petitioner also objects to Exhibit 2001 to the extent it relies on an exhibit containing an out of court statements for their truth, thus constituting impermissible hearsay. *See* FRE 801-804. Petitioner also objects to Exhibits 2051-2054 to the extent they rely on or cite a document lacking proper authentication. *See* FRE 901-902.

Petitioner further objects to any portion of Exhibits 2051-2054 that relies on or cites to an Exhibit listed below in Table 1 for the same reasons included in Table 1 for that Exhibit. Petitioner further objects to Patent Owner's exhibits and Patent Owner's reliance on them for the reasons set forth below in Table 1 and the Objection Key.

Table 1.

No.	Exhibit	Objections
1022	Prosecution History of the '628 patent, in particular the Declaration of Dr. Charles L. Beach under 37 C.F.R. § 1.132 ("Beach Decl.")	F
2001	Declaration of Dr. Corey Berkland	H
2002	U.S. Food and Drug Admin., FDA approves Onureg® (azacytidine tablets) for acute myeloid leukemia (2020), https://www.fda.gov/drugs/resources-information-	B, C, D, E, H

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No.	Exhibit	Objections
	approved-drugs/fdaapproves-onureg-azacitidine-tablets-acute-myeloid-leukemia ("FDA Approves Onureg®")	
2006	Canadian Product 200mg Onureg® Product Information	B, C, D, E, G, H
2007	Canadian Product 300mg Onureg® Product Information	B, C, D, E, G, H
2008	Canadian Product Monograph Onureg®	B, C, D, E, G, H
2013	European Commission Decision 17.6.21	B, C, D, E, H
2016	FASTtrack 2010 ("FASTtrack")	B, C, D, E, H
2023	National Cancer Institute, Bioassay of 5-azacytidine for Possible Carcinogenicity, U.S. DEP'T OF HEALTH, EDUC., AND WELFARE (1978) ("National Cancer Institute")	A, C, D, E, H
2025	Onureg® Label	B, C, D, E, H
2026	International Pat. Appl. Pub. No. WO2009/139888 ("WO2009/139888")	B, C, D, E, H
2028	REMINGTON, THE SCIENCE AND PRACTICE OF PHARMACY 802–938 (21st Ed. 2005) ("Remington 2005")	C, D, E, F, G
2030	U.S. Pat. Pub. No. US20040186065A1 ("Ionescu-065")	C, D, E, H
2035	U.S. Pat. No. 6,887,855 ("Ionescu-855")	C, D, E, H
2036	U.S. Pat. No. 7,078,518 ("Ionescu-518")	C, D, E, H
2037	U.S. Pat. No. 7,772,199 ("Ionescu-199")	C, D, E, H
2038	U.S. Pat. Pub. No. US20060247189 ("Ionescu-189")	C, D, E, H
2039	U.S. Pat. Pub. No. US20100298253 ("Ionescu-253")	B, C, D, E, H
2040	Ward, M., et al., An oral dosage formulation of azacytidine: A pilot pharmacokinetic study, J. OF CLINICAL ONCOLOGY (2007) ("Ward")	C, D, E
2041	International Pat. Appl. Pub. No. WO2008/028193 ("WO2008/028193")	B, C, D, E, F
2042	Gibson, M., Pharm. PREFORMULATION AND FORMULATION: A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 1-11 (2001) ("Gibson Supplemental")	A, C, D, H
2043	Lieberman, H., et al., PHARMACEUTICAL DOSAGE FORMS 2 (2nd Ed. 1990) ("Lieberman Vol. 2")	C, D, E, H
2044	International Pat. Appl. Pub. No. WO2004/082618 ("WO2004/082618")	C, D, E
2047	Savage 1967 ("Savage")	C, D, E, H
2048	Pawar, et al., <i>Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to</i>	B, C, D, F

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No.	Exhibit	Objections
	<i>Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: A Carbamazepine Case Study</i> , 25 AAPS J. 67 (2023) ("Pawar")	
2049	Deposition Transcript of Hannah K. Batchelor ("Batchelor Tr.")	Petitioner incorporates by reference and reiterate the objections made on the record during the deposition
2050	Deposition Transcript of Graham Buckton, Ph.D. ("Buckton Tr.")	Petitioner incorporates by reference and reiterate the objections made on the record during the deposition. Additionally, Exhibit 2050 is incomplete because it does not include the errata that was timely returned.
2055	U.S. Food and Drug Admin., <i>FDA approves Onureg® (azacytidine tablets) for acute myeloid leukemia</i> (2020), https://www.fda.gov/drugs/resources-information-approved-drugs/fdaapproves-onureg-azacitidine-tablets-acute-myeloid-leukemia ("FDA Approves Onureg®")	B, C, D, E, F, G
2056	Canadian Product 200mg Onureg Product Information	B, C, D, E, F
2057	Canadian Product 300mg Onureg Product Information	B, C, D, E, F, G
2058	Canadian Product Monograph Onureg	B, C, D, E, F, G
2059	European Commission Decision 17.6.21	B, C, D, E, F, G
2060	Perrie, Y. & Rades, T., PHARMACEUTICAL: DRUG DELIVERY AND TARGETING (2010) ("FASTtrack")	B, C, D, E, F, G

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No.	Exhibit	Objections
2062	Onureg® Label	B, C, D, E, F, G
2063	Gibson, M., Pharm. PREFORMULATION AND FORMULATION: A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 1-11 (2001) ("Gibson Supplemental")	A, C, D, E, F
2064	Altman, R, & Sarg, M., CANCER DICTIONARY: REVISED EDITION 16–17, 197 (2000) ("Altman")	C, D, E, F
2065	Allen, L, Et Al., ANSEL'S PHARM. DOSAGE FORMS AND DRUG DELIVERY SYS. (8th Ed. 2005) ("Ansel")	C, D, E, F
2066	Antonsson, B., et al., <i>Effect of 5-Azacytidine and Congeners on DNA Methylation and Expression of Deoxycytidine Kinase in the Human Lymphoid Cell Lines CCRF/CEM/0 and CCRF/CEM/dCk⁻¹</i> , 47 CANCER RESEARCH 3762–78 (1987) ("Antonsson")	C, D, E, F
2067	Aulton, M., PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN (1988) ("Aulton")	C, D, E, F
2068	Bankhead, C., <i>Year in Review: Acute Myeloid Leukemia</i> , MedPage Today (Nov. 29, 2020), https://www.medpagetoday.com/hematologyoncology/leukemia/89909 ("Bankhead")	B, C, D, E, F
2070	Ben-Kasus, T., et al., <i>Metabolic activation of zebularine, a novel DNA methylation inhibitor, in human bladder carcinoma cells</i> , 70 BIOCHEM. PHARM. 121–33 (2005) ("Ben-Kasus")	C, D, E, F
2071	Carter, J., et al., <i>Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy</i> , 5 SIGNAL TRANSDUCTION AND TARGETED THERAPY 288 (2020) ("Carter")	B, C, D, E, F
2072	Choi, Y., et al., <i>Oral Maintenance Chemotherapy with 6-Mercaptopurine and Methotrexate in Patients with Acute Myeloid Leukemia Ineligible for Transplantation</i> , 30 KOREAN ACADEMY OF MED. SCI. 1416–22 (2015) ("Choi")	B, C, D, E, F
2073	Cogle, C., et al., <i>Oral Azacitidine (CC-486) for the Treatment of Myelodysplastic Syndromes and Acute Myeloid Leukemia</i> , 20 ONCOLOGIST 1404–12 (2015) ("Cogle")	B, C, D, E, F

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No.	Exhibit	Objections
2074	Covey, J., et al., <i>Differences in DNA Damage Produced by Incorporation of 5-Aza-2'-deoxycytidine or 5,6-Dihydro-5-azacytidine into DNA of Mammalian Cells</i> , 46 CANCER RESEARCH 5511–17 (1986) (“Covey”)	C, D, E, F
2075	Craig, C. & Stitzel, R., MODERN PHARMACOLOGY WITH CLINICAL APP. (6th Ed. 2004) 48–55 (“Craig”)	C, D, E, F
2076	Curtiss, F., <i>Pharmacy Benefit Spending on Oral Chemotherapy Drugs</i> , 12 J. OF MANAGED CARE PHARMACY 570–77 (2006) (“Curtiss”)	C, D, E, F
2077	DeSimone, J., et al., <i>Tetrahydrouridine, Cytidine, Analogues, and Hemoglobin F</i> , 18 AM. J. OF HEMATOLOGY 283–88 (1985) (“DeSimone”)	C, D, E, F
2078	Dressman, J., et al., <i>Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms</i> , 15 PHARM. RESEARCH 11–22 (1998) (“Dressman”)	C, D, E, F
2079	Case Reports, 72 BRITISH J. OF HAEMATOLOGY 467–68 (1989) (“Dunbar”)	C, D, E, F
2080	Ellison, R., et al., <i>Arabinosyl Cytosine: A Useful Agent in the Treatment of Acute Leukemia in Adults</i> , 32 J. OF HEMATOLOGY 507–23 (1968) (“Ellisson”)	C, D, E, F
2081	The ASCO Post Staff, “FDA Approves Oral Azacitidine as Maintenance Therapy for Adults With AML in First Remission” (Sept. 25, 2020), https://ascopost.com/issues/september-25-2020/fdaapproves-oral-azacitidine-as-maintenance-therapy-for-adults-withaml-in-first-remission/ (“FDA Approves Oral Azacitidine”)	B, C, D, E, F
2082	Frisch, A., et al., <i>How we treat older patients with acute myeloid leukaemia</i> , 191 BRITISH J. OF HAEMATOLOGY 682–91 (2020) (“Frisch”)	B, C, D, E, F
2083	Futterman, B., et al., <i>Studies on the Cytostatic Action Phosphorylation and Deamination of 5-Azacytidine and 5,6-Dihydro-5-Azacytidine in Hela Cells</i> , 27 BIOCHEM. PHARM. 907–9 (1978) (“Futterman”)	C, D, E, F
2084	Garcia-Manero, G., et al., <i>Phase I Study of Oral Azacitidine in Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Acute Myeloid</i>	B, C, D, E, F

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No.	Exhibit	Objections
	<i>Leukemia</i> , 29 J. OF CLIN. ONCOLOGY 2521–27 (2011) (“Garcia-Manero”)	
2085	Goldin, A., et al., <i>Relation of Structure of Purine and Pyrimidine Nucleosides to Antitumor Activity</i> , 1 CANCER CHEMOTHERAPY 1–29, 268 (1968) (“Goldin”)	A, C, D, E, F, G
2086	Griffiths, E., <i>Oral hypomethylating agents: beyond convenience in MDS</i> , 2021 HEMATOLOGY 439–47 (2021) (“Griffiths”)	B, C, D, E, F
2087	Grønbaek, K., et al., <i>Epigenetic Changes in Cancer as Potential Targets for Prophylaxis and Maintenance Therapy</i> , 103 BASIC & CLINICAL PHARM. & TOXICOLOGY 389–96 (2008) (“Grønbaek”)	C, D, E, F
2088	Hrodek, O. & Vesely J., <i>5-Azacytidine in Childhood Leukemia</i> , 18 NEOPLASMA 493–503 (1971) (“Hrodek”)	C, D, E, F
2089	Kantarjian, H., et al., <i>Acute Myeloid Leukemia: Historical Perspective and Progress in Research and Therapy Over 5 Decades</i> , 21 CLIN. LYMPHOMA, MYELOMA AND LEUKEMIA 580–97 (2021) (“Kantarjian”)	B, C, D, E, F
2090	Karon, M., et al., <i>5-Azacytidine: A New Active Agent for the Treatment of Acute Leukemia</i> , 42 BLOOD 359–65 (1973) (“Karon”)	C, D, E, F
2091	Kipp, D. & Wei, A., <i>The path to approval for oral hypomethylating agents in acute myeloid leukemia and myelodysplastic syndromes</i> , 17(20) FUTURE ONCOL. 2563–71 (2021) (“Kipp”)	B, C, D, E, F
2092	Kornblith, A., et al., <i>Impact of Azacytidine on the Quality of Life of Patients With Myelodysplastic Syndrome Treated in a Randomized Phase III Trial: A Cancer and Leukemia Group B Study</i> , 20 J. OF CLIN. ONCOLOGY 2441–52 (2002) (“Kornblith”)	C, D, E, F
2093	Lammers, P. & Cashen, A., <i>Azacytidine: A Review of its Use in the Management of Myelodysplastic Syndromes</i> , 1 CLIN. MED. THERAPEUTICS 1189–97 (2009) (“Lammers”)	B, C, D, E, F

Petitioner's Second Set of Objections to Evidence

No.	Exhibit	Objections
2094	Lin, R., <i>Allogeneic Transplantation for Older Patients with Acute Myeloid Leukemia: The Dawn of a New Era</i> , 28 TRANSPLANTATION AND CELLULAR THERAPY 793–94 (2022) (“Lin 2022”)	B, C, D, E, F
2095	Liu, H., <i>Emerging agents and regimens for AML</i> , 14 J. HEMATOLOGY & ONCOLOGY 19 (2021) (“Liu”)	B, C, D, E, F
2096	Lomen, V., et al., “Phase I Study of 5-Azacytidine Using 24 Hrs Continuous Infusion for 5 Days” 16 PROCEEDINGS OF THE AM. ASS. FOR CANCER RESEARCH & AM. SOC. OF CLIN. ONCOLOGY 52 (Mar. 1975) (“Lomen”)	C, D, E, F
2097	Löwenberg, B., et al., <i>Mitoxantrone Versus Daunorubicin in Induction-Consolidation Chemotherapy</i> , 16 J. OF CLIN. ONCOLOGY 872–81 (1998) (“Löwenberg”)	C, D, E, F
2098	Ma, X., et al., <i>Myelodysplastic Syndromes: Incidence and Survival in the United States</i> , 109 AM. CANCER SOC. 1536–42 (2007) (“Ma”)	C, D, E, F
2100	McCredie, K., <i>Treatment of Acute Leukemia with 5-Azacytidine (NSC-102816)</i> , 57 CANCER CHEMOTHERAPY REP. 319–23 (1973) (“McCredie”)	C, D, E, F
2101	Neil, G., et al., <i>Enhancement by Tetrahydrouridine (NSC-112907) of the Oral Activity of 5-Azacytidine (NSC-102816) in L1210 Leukemic Mice</i> , 59 CANCER CHEMOTHERAPY REP. 459–65 (1975) (“Neil”)	C, D, E, F
2102	Odenike, O., <i>Incorporating novel approaches in the management of MDS beyond conventional hypomethylating agents</i> , AM. SOC. OF HEMATOLOGY 460–69 (2017) (“Odenike”)	B, C, D, E, F, G
2103	Goodman, A., “Oral CC-486 Maintenance Therapy Extends Survival in Older Patients with AML” THE ASCO POST (Jan. 25, 2020), https://ascopost.com/issues/january-25-2020/oral-cc-486-maintenancetherapy-extends-survival-in-older-patients-with-aml/ (“Oral CC-486”)	B, C, D, E, F
2104	Perl, A., <i>The role of targeted therapy in the management of patients with AML</i> , 1 BLOOD ADVANCES AND HEMATOLOGY 2281–94 (2017) (“Perl”)	B, C, D, E, F

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No.	Exhibit	Objections
2107	Porta, M., A DICTIONARY OF EPIDEMIOLOGY 226–27 (5th Ed. 2008) (“Porta”)	A, B, C, D, E, F
2108	Preisler, H., et al., <i>Comparison of Three Remission Induction Regimens and Two Postinduction Strategies for the Treatment of Acute Nonlymphocytic Leukemia</i> , 69 BLOOD 1441–49 (1987) (“Preisler”)	C, D, E, F
2110	Récher, C., <i>The beginning of a new therapeutic era in acute myeloid leukemia</i> , 2 J. HAEMATOLOGY 823–33(2021) (“Récher”)	B, C, D, E, F
2111	Reville, P., <i>Maintenance Therapy in AML</i> , 10 FRONTIERS IN ONCOLOGY (2021) (“Reville”)	B, C, D, E, F
2112	Shnider, B., et al., <i>A Phase I Study of 5-Azacytidine (NSC-102816)</i> , 16(4) J. OF CLIN. PHARMACOLOGY 205–12 (1976) (“Shnider”)	C, D, E, F
2114	Slater, H., <i>Phase 3 QUAZAR AML-001 Trial Finds Oral Azacitidine Extends Survival in Older Adults with AML</i> , Cancer Network (Jan. 12, 2021) (“Slater”)	B, C, D, E, F
2115	Sochacka-Ćwikła, A., et al., <i>FDA-Approved Drugs for Hematological Malignancies—The Last Decade Review</i> , 14 CANCERS 87 (2022) (“Sochacka-Ćwikła”)	B, C, D, E, F
2116	Sorm, F., et al., <i>5-Azacytidine, a New, Highly Effective Cancerostatic</i> , 20 INSTITUTE OF ORGANIC CHEM. AND BIOCHEM. 202–3 (1964) (“Sorm”)	C, D, E, F
2118	Sorrentino, V., et al., <i>Hypomethylating Chemotherapeutic Agents as Therapy for Myelodysplastic Syndromes and Prevention of Acute Myeloid Leukemia</i> , 14 PHARMACEUTICALS 641 (2021) (“Sorrentino”)	B, C, D, E, F
2119	Southall, J., “Oral azacytidine extends survival for patients with AML in remission after chemotherapy” HemOncToday (Jan. 5, 2021) (“Southall”)	B, C, D, E, F
2120	Steensma, D., <i>ASH 2010 Meeting Report—Top 10 clinically-oriented abstracts in myelodysplastic syndromes (MDS)</i> , 86 AM. J. OF HEMATOLOGY 385–91 (2011) (“Steensma”)	B, C, D, E, F

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No.	Exhibit	Objections
2121	Surbone, A., et al., <i>Phase I and Pharmacokinetic Study of Arabinofuranosyl-5-azacytosine (Fazarabine, NSC 281272)</i> , 50 CANCER RESEARCH 1220–25 (1990) (“Surbone”)	C, D, E, F
2122	Toutain, P. & Bousquet-Melou, A., <i>Bioavailability and its assessment</i> , 27 J. VET. PHARMACOLOGY. THERAP. 455–66 (2004) (“Toutain”)	C, D, E, F
2123	U.S. Provisional 60/824320 File History (“60/824,320”)	B, C, D, E, F
2124	U.S. Patent Application US 2008/0057086 (“US2008/0057086”)	B, C, D, E, F
2125	Vigil, C., et al., <i>Safety and efficacy of azacitidine in myelodysplastic syndromes</i> , 4 DRUG DESIGN, DEVELOPMENT AND THERAPY 221–29 (2010) (“Vigil”)	B, C, D, E, F
2126	Vogler, W., et al., “Remission Induction in Refractory Myeloblastic Leukemia with Continuous Infusion of 5-Azacitidine” 16 PROCEEDINGS OF THE AM. ASS. FOR CANCER RESEARCH & AM. SOC. OF CLIN. ONCOLOGY 155 (Mar. 1975) (“VoglerI”)	C, D, E, F
2127	Vogler, W., <i>5-Azacitidine (NSC 102816): A New Drug for the Treatment of Myeloblastic Leukemia</i> , 48 BLOOD 331–37 (1976) (“VoglerII”)	C, D, E, F
2128	Von Hoff, D., et al., <i>5-Azacitidine A New Anticancer Drug with Effectiveness in Acute Myelogenous Leukemia</i> , 85 ANNALS OF INTERNAL MEDICINE 237–45 (1976) (“VonHoff”)	C, D, E, F
2129	Wei, A., et al., <i>Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first remission after chemotherapy</i> , 98 AM. J. OF HEMATOLOGY E84–87 (2023) (“Wei”)	B, C, D, E, F
2130	Weill Cornell Medicine, “New maintenance treatment for acute myeloid leukemia prolongs the lives of patients” NEW ENGLAND J. OF MED. (Jan. 22, 2021), https://news.weill.cornell.edu/news/2021/01/new-maintenancetreatment-for-acute-myeloid-leukemia-prolongs-the-lives-of-patients , (“Weill Cornell”)	B, C, D, E, F

Petitioner's Second Set of Objections to Evidence

No.	Exhibit	Objections
2131	Zielinski, W. & Sprinzl, M., <i>Chemical synthesis of 5-azacytidine nucleotides and preparation of tRNAs containing 5-azacytidine in its 3'-terminus</i> , 12 NUCLEIC ACIDS RESEARCH 5025–36 (1984) (“Zielinski”)	C, D, E, F
2132	Ziemba, A., et al., <i>Development of an Oral Form of Azacytidine: 2'3'5Triacetyl-5-Azacytidine</i> , 2011 CHEMOTHERAPY RESEARCH AND PRACTICE 1–9 (2011) (“Ziemba”)	B, C, D, E, F
2133	Exemestane Label (“Exemestane”)	B, C, D, E, F, G
2134	Anastrozole Label (“Anastrozole”)	B, C, D, E, F, G
2135	Letrozole Label (“Letrozole”)	B, C, D, E, F, G
2136	Blum W, et al., <i>Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B Study (CALGB 10503)</i> , 31 LEUKEMIA 34–39 (2017) (“Blum”)	B, C, D, E, F
2137	Cytarabine Label (“Cytarabine”)	B, C, D, E, F, G
2138	Dacogen Label (“Dacogen”)	B, C, D, E, F, G
2139	Mitoxantrone Label (“Mitoxantrone”)	B, C, D, E, F, G
2140	Finkel, M., <i>The Orphan Drug Act and the Federal Government's Orphan Products Development Program</i> , 99 PUBLIC HEALTH REPS. 313–16 (1984) (“Finkel”)	C, D, E, F
2141	Martinez, M. & Amidon, G., <i>A Mechanistic Approach to Understanding the Factors Affecting Drug Absorption</i> , 42 J. OF CLIN. PHARMACOLOGY 620–43 (2002) (“Martinez”)	C, D, E, F
2142	European Medicines Agency, <i>Assessment Report of Onureg</i> EMA/308711/2021 (“European Medicines Report”)	B, C, D, E, F, G
2143	Hirayama, H., et al., <i>Distribution and Excretion of Cyclocytidine in Monkeys, Dogs, and Rats</i> , 65 GANN 153–61 (1974) (“Hirayama”)	C, D, E, F
2144	Lieberman, H., et al., <i>PHARMACEUTICAL DOSAGE FORMS: TABLETS 1</i> (2nd Ed. 1989) (“Lieberman Vol. 1”)	C, D, E, F
2145	Dean, D., et al., <i>PHARMACEUTICAL PACKAGING TECHNOLOGY</i> (2000) (“Dean”)	C, D, E, F

Petitioner's Second Set of Objections to Evidence

No.	Exhibit	Objections
2146	Gennaro, A., REMINGTON'S PHARMACEUTICAL SCIENCES 257–309, 1519–44, 1615–32 (18th Ed. 1990) (“Remington 1990”)	C, D, E, F,
2147	REMINGTON, THE SCIENCE AND PRACTICE OF PHARMACY 319–37, 702–19, 745–75, 1025–36 (21st Ed. 2005) (“Remington 2005 II”)	C, D, E, F, G
2148	Gibaldi, M. & Perrier, D., PHARMACOKINETICS (2nd Ed. 2007) 271–353 (“Gibaldi”)	C, D, E, F
2150	Huls, G., et al. <i>Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients</i> , 133 BLOOD, THE JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY 1457–64 (2019) (“Huls”)	B, C, D, E, F

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Objection Key:

- A: FRE 106 (incomplete) the document is an incomplete writing.
- B: FRE 401/402/403 (relevance) the document is not relevant to any issue in this IPR proceeding beyond purported unexpected results, industry praise, skepticism, or satisfaction of a long-felt need (but not the existence of a long-felt need) because the purported date of the document is after the priority date of the '628 patent.
- C: FRE 401/402 (relevance) the document is not relevant to any issue in this IPR proceeding.
- D: FRE 403 (unduly prejudicial, waste of time, confusing) the document is not relevant to any issue in the IPR proceeding because any probative value is substantially outweighed by the danger of undue prejudice, confusing the issues, undue delay, misleading the factfinder, or wasting time.
- E: FRE 403 (cumulative) the document is not relevant to any issue in the IPR proceeding because any probative value is substantially outweighed by the danger of needlessly presenting cumulative evidence.
- F: FRE 801-804 (hearsay) the document contains out of court statements that Patent Owner relies on for their truth, thus constituting impermissible hearsay.
- G: FRE 901-902 the document lacks proper authentication and is not self-authenticating.
- H: Not relied upon by any expert cited in Patent Owner's Response or cited in Patent Owner's Response.

Petitioner's Second Set of Objections to Evidence

Dated: October 19, 2023

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Petitioner's Second Set of Objections to Evidence

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing: PETITIONER'S SECOND SET OF OBJECTIONS TO PATENT OWNER'S EVIDENCE by email to the electronic service addresses for Patent Owner:

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