

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner

Case IPR2023-00512
Patent 8,846,628

PATENT OWNER'S RESPONSE

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2122	Toutain, P. & Bousquet-Melou, A., <i>Bioavailability and its assessment</i> , 27 <i>J. VET. PHARMACOLOGY. THERAP.</i> 455–66 (2004) (“Toutain”)
2123	U.S. Provisional 60/824320 File History (“60/824,320”)
2124	U.S. Patent Application US 2008/0057086 (“US2008/0057086”)

No.	Exhibit
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”)
2126	Vogler, W., et al., “Remission Induction in Refractory Myeloblastic Leukemia with Continuous Infusion of 5-Azacytidine” 16 PROCEEDINGS OF THE AM. ASS. FOR CANCER RESEARCH & AM. SOC. OF CLIN. ONCOLOGY 155 (Mar. 1975) (“VoglerI”)
2127	Vogler, W., <i>5-Azacytidine (NSC 102816): A New Drug for the Treatment of Myeloblastic Leukemia</i> , 48 BLOOD 331–37 (1976) (“VoglerII”)
2128	Von Hoff, D., et al., <i>5-Azacytidine A New Anticancer Drug with Effectiveness in Acute Myelogenous Leukemia</i> , 85 ANNALS OF INTERNAL MEDICINE 237–45 (1976) (“VonHoff”)
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”)
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-maintenance-treatment-for-acute-myeloid-leukemia-prolongs-the-lives-of-patients , (“Weill Cornell”)
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”)
2132	Ziemba, A., et al., <i>Development of an Oral Form of Azacytidine: 2'3'5'Triacetyl-5-Azacytidine</i> , 2011 CHEMOTHERAPY RESEARCH AND PRACTICE 1–9 (2011) (“Ziemba”)

No.	Exhibit
2133	Exemestane Label (“Exemestane”)
2134	Anastrozole Label (“Anastrozole”)
2135	Letrozole Label (“Letrozole”)
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”)
2137	Cytarabine Label (“Cytarabine”)
2138	Dacogen Label (“Dacogen”)
2139	Mitoxantrone Label (“Mitoxantrone”)
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”)
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”)
2142	European Medicines Agency, Assessment Report of Onureg EMA/308711/2021(“European Medicines Report”)
2143	Hirayama, H., et al., <i>Distribution and Excretion of Cyclocytidine in Monkeys, Dogs, and Rats</i> , 65 GANN 153–61 (1974) (“Hirayama”)
2144	LIEBERMAN, H., ET AL., PHARMACEUTICAL DOSAGE FORMS: TABLETS 1 (2nd Ed. 1989) (“Lieberman Vol. 1”)
2145	DEAN, D., ET AL., PHARMACEUTICAL PACKAGING TECHNOLOGY (2000) (“Dean”)

No.	Exhibit
2146	GENNARO, A., REMINGTON'S PHARMACEUTICAL SCIENCES 257–309, 1519–44, 1615–32 (18th Ed. 1990) (“Remington 1990”)
2147	REMINGTON, THE SCIENCE AND PRACTICE OF PHARMACY 319–37, 702–19, 745–75, 1025–36 (21st Ed. 2005) (“Remington 2005 II”)
2148	GIBALDI, M. & PERRIER, D., PHARMACOKINETICS (2nd Ed. 2007) 271–353 (“Gilbaldi”)
2149	First Expert Declaration of James L. Mullins, Ph.D.
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”)
2151	Second Expert Declaration of James L. Mullins, Ph.D.

I. INTRODUCTION

This proceeding involves a challenge to U.S. Patent No. 8,846,628 (“the ’628 patent”), which claims pharmaceutical compositions and methods of treatment using orally administered 5-azacytidine in a non-enteric coated tablet. 5-azacytidine and its anticancer properties have been known since the 1960s. However, the drug was known to readily break down in water and be quickly metabolized in the body by an enzyme called cytidine deaminase. The drug’s instability made it difficult to develop a usable therapeutic formulation of 5-azacytidine. Indeed, it took 40 years after 5-azacytidine’s initial discovery before *any* use of the drug received FDA approval. And even then, a suitable, orally administered formulation proved elusive. 5-azacytidine was approved only for administration as an injectable formulation, which had significant drawbacks in terms of patient comfort and compliance.

Before the invention of the ’628 patent, nobody believed it would be possible to develop a therapeutically effective, non-enteric coated tablet of 5-azacytidine for oral administration—not even the inventors of the ’628 patent. Indeed, the inventors made the critical discovery underlying the ’628 patent serendipitously while studying *enterically* coated tablets. Through a mistake in the manufacturing process, the inventors hypothesized they could administer a therapeutically effective amount of 5-azacytidine using a non-enteric coated tablet.

The results of their research are described and claimed in the '628 patent, and ultimately resulted in the drug Onureg®—which was first approved by the FDA in 2020 and remains the only FDA-approved orally administered formulation of 5-azacytidine.

The Petition ignores the substantial challenges to developing an orally administered formulation of 5-azacytidine, which frustrated research efforts for decades. Instead, the Petition relies on the prophetic disclosure of a “sugar-coated” tablet formulation of 5-azacytidine in a prior art patent application (Ionescu) to argue anticipation. But a sugar-coating is not synonymous with a non-enteric coating, and the Petition does not identify *any* disclosure of a non-enteric coated tablet in Ionescu, which is fatal to Petitioner's anticipation challenge in Ground 1.

Petitioner's obviousness challenges in Grounds 2 and 3 fare no better. The Petition repeatedly asserts that a POSA would have arrived at the claimed invention by following the supposedly “default” approach. But Petitioner cannot rely on notions of what would have been the default as a substitute for actual evidence tied to what was known about 5-azacytidine. And none of the supposedly default choices underlying Petitioner's obviousness theory can be reconciled with what was known about 5-azacytidine at the time of the invention, particularly the drug's known chemical and enzymatic instability. Indeed, it cannot be that an orally administered formulation that took *decades* to develop was obvious by

making default choices. And the fact that the drug first was approved as an *injectable* formulation confirms that the orally administered formulation claimed in the '628 patent was not the default option. Petitioner's assertions to the contrary are pure hindsight.

Because Petitioner has failed to meet its burden to show anticipation or obviousness, Patent Owner respectfully requests that the Board uphold the validity of the challenged claims.

II. BACKGROUND

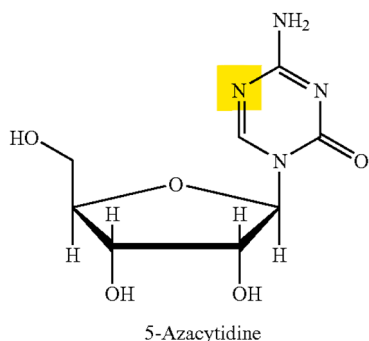
A. MDS and AML

This IPR involves a treatment for two blood disorders: acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Ex.1001('628 patent), 1:39-64; Ex.1017(Marcucci), 597; Ex.2053(Blum Decl.), ¶¶11-12. Both MDS and AML are serious conditions with limited treatment options and ultimately lead to death in the majority of patients. Ex.2092(Kornblith), 2441; Ex.2098(Ma), Abstract; Ex.2053(Blum Decl.), ¶¶11-12. For most MDS patients, the disease ultimately progresses to death. Ex.1001('628 patent), 1:39-64; Ex.1017(Marcucci), 597; Ex.2053(Blum Decl.), ¶11. AML, which results in rapid, unregulated growth of immature blood cells in the bone marrow, has the lowest survival rate of all acute leukemia types with three-quarters of patients dying within five years. Ex.2064(Altman), 16-17; Ex.2072(Choi), 1416;

Ex.2073(Cogle), 1405; Ex.2053(Blum Decl.), ¶12. Before the invention of the '628 patent, the FDA had only approved one oral therapy to treat MDS and no oral or maintenance therapies for AML. Ex.2067(Curtiss), 573; Ex.2071(Carter); Ex.2136(Blum), Abstract; Ex.2053(Blum Decl.), ¶13; Ex.2051(Berkland Decl.), ¶30.

B. 5-Azacytidine

5-azacytidine is a compound similar to cytidine, which is a component of DNA and RNA, except it has a nitrogen atom in place of a carbon atom, which is highlighted in the structure below. Ex.1001('628 patent), 2:37-62; Ex.2054(Etter Decl.), ¶10.



Ex.1001('628 patent), 2:48-62. After administration of 5-azacytidine, cancer cells incorporate it into DNA and RNA. *Id.*, 3:9-27. When incorporated, 5-azacytidine “restor[es] normal functions” by promoting “re-expression of genes involved in normal cell cycle regulation, differentiation and death” leading to “the death of rapidly dividing cells, including cancer cells....” *Id.*, 3:9-22; Ex.2051(Berkland Decl.), ¶31; Ex.2054(Etter Decl.), ¶11.

C. The Known Challenges to Developing a Therapeutically Effective Formulation of 5-Azacytidine

Researchers have studied 5-azacytidine as a potential anti-cancer drug since it was first synthesized in the 1960s. Ex.1024(Pi'skala); Ex.2116(Sorm); Ex.2012(Čihák); Ex.2027(Pit'hová); Ex.2085(Goldin); Ex.2054(Etter Decl.), ¶11; Ex.2051(Berkland Decl.), ¶¶32-33; *see also* Ex.2128(VonHoff), 237; Ex.2088(Hrodek); Ex.2112(Shnider); Ex.2096(Lomen); Ex.2100(McCredie). However, 5-azacytidine presented two significant problems for a POSA that limited its therapeutic use.

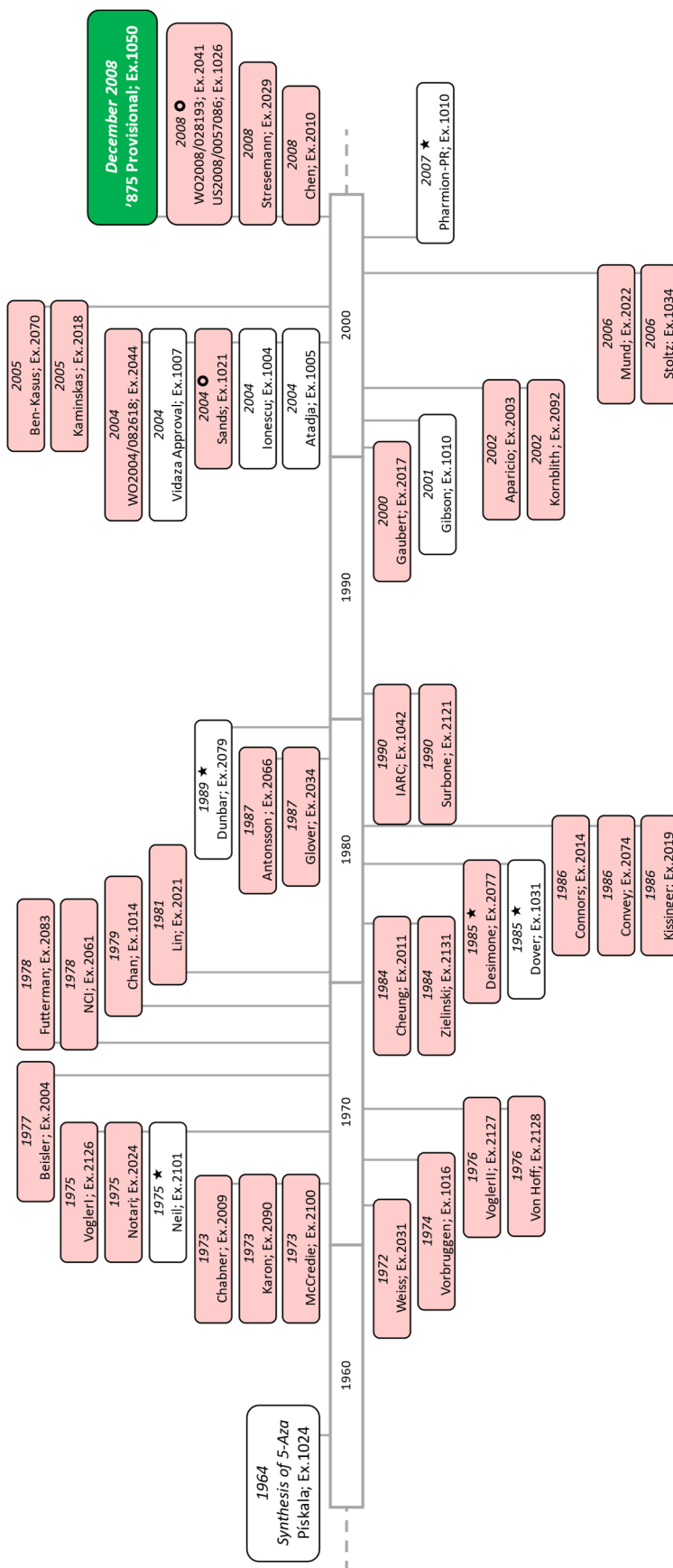
First, 5-azacytidine was understood to be unstable and rapidly break down when exposed to water through a process called “hydrolysis.” Ex.2128(VonHoff), 238, 239-240, Table 1; Ex.2031(Weiss), 413-414, 418; *see also* Ex.2051(Berkland Decl.), ¶34 (citing Ex.2090(Karon); Ex.2100(McCredie); Ex.2127(VoglerII); Ex.2054(Etter Decl.), ¶¶12-13.

Second, 5-azacytidine was known to be broken down by an enzyme called “cytidine deaminase,” which renders the drug ineffective. Ex.2009(Chabner), 2763, 2765; Ex.2054(Etter Decl.), ¶14; Ex.2051(Berkland Decl.), ¶35.

Faced with these challenges, researchers suggested strategies including using more stable prodrugs of 5-azacytidine or combining 5-azacytidine with enzymatic inhibitors. Ex.2041(WO2008/028193), ¶¶[0007], [0008]-[0011]; Ex.2054(Etter Decl.), ¶¶22-25. But these strategies had only “limited success.” *See* Paper

7(DOI), 46 (characterizing Ex.1031(Dover); *see also* Ex.2051(Berkland Decl.), ¶37; Ex.2101(Neil); Ex.2077(DeSimone); Ex.2079(Dunbar); Ex.2054(Etter Decl.), ¶20. After decades of failure, many gave up on 5-azacytidine as a treatment, and by 1987 even the NIH acknowledged that the drug had no “definitive role.” Ex.2034(Glover), 742; Ex.2051(Berkland Decl.), ¶38.

The literature is replete with the challenges with formulating 5-azacytidine into a therapeutically effective dosage form. Indeed, these issues were identified in the earliest papers describing the drug in the 1970s and continued up to the filing of the application for the '628 patent in December 2008. Ex.2051(Berkland Decl.), ¶¶32, 36-40; *see also* Ex.1014(Chan), 807; Ex.2024(Notari); 1157; Ex.2021(Lin), 1229; Ex.2074(Covey); Ex.2011(Cheung), 1159; Ex.2131(Zielinski), 5029; Ex.2121(Surbone), 1220; Ex.2083 Futterman), 907; Ex.2066(Antonsson), 3672; Ex.2003(Aparicio), 632; Ex.2070(Ben-Kasus), 130; Ex.2017(Gaubert), 1011-1012. The timeline below summarizes the literature describing the long history of 5-azacytidine's development and illustrates in pink that the majority of references describe 5-azacytidine's chemical and/or enzymatic instability. Ex.2051(Berkland Decl.), ¶32.



- Disclosures of instability (e.g., hydrolysis and/or enzymatic metabolism)
- ★ Documents characterized by Petitioner or Board as disclosing an attempted oral formulation
- Disclosures of enteric-coated tablet formulations

D. The Therapeutic Use of 5-Azacytidine

1. Injectable 5-azacytidine

The challenges to administering a therapeutically effective dose of 5-azacytidine were initially addressed by developing an injectable formulation. Ex.1007(Vidaza® Label 2004). By quickly administering the drug after reconstituting it in water, it was possible to achieve a therapeutic pharmacokinetic profile before hydrolysis, metabolism, and degradation eliminated the drug. Ex.1007(Vidaza® Label 2004), 0008, 0023-0024; Ex.2018(Kaminskas), 176; Ex.2054(Etter Decl.), ¶16. This 5-azacytidine injectable formulation was approved by the FDA in 2004 and is marketed as Vidaza®. Ex.1007(Vidaza® Label 2004); Ex.2054(Etter Decl.), ¶15; Ex.2051(Berkland Decl.), ¶41.

2. Oral 5-azacytidine

Although Vidaza® represented a significant advance in patient care, it also presented challenges. For example, the process of administering 5-azacytidine by injection requires a large volume of liquid and causes discomfort. Ex.1007-0018-0021(Vidaza® Label 2004); Ex.1017-0002(Marcucci); Ex.2125(Vigil), 227; Ex.2053(Blum), ¶¶32, 45. There is a risk of injection site infections. Ex.2118(Sorretino), 4, 20. Administering 5-azacytidine by injection is also a significant burden on patients and caregivers, who need to travel to a doctor's office to receive the injection daily for seven days with additional four-week

cycles. Ex.1007-0018-0021(Vidaza® Label 2004); Ex.2076(Curtiss), 570, 573, 575; Ex.2053(Blum), ¶44; Ex.2054(Etter Decl.), ¶18.

Therefore, even after Vidaza®'s approval, there remained a medical need to develop an oral formulation of 5-azacytidine to overcome the challenges of administering the drug by injection. Ex.2053(Blum), ¶¶14-15. Although several researchers attempted to develop an oral formulation, the “short half-life in aqueous solutions and low oral bioavailability” of 5-azacytidine stymied those efforts. Ex.2132(Ziemba), 2; Ex.1019(Redkar), ¶[0106]; Ex.2010(Chen), 21; Ex.2022(Mund), 8; Ex.2018(Kaminskas), 177; Ex.2029(Stresemann), 8; Ex.2051(Berkland Decl.), ¶¶43-44. In fact, in 2008, the art suggested that an *enteric* coating should be used for 5-azacytidine due to its known instability and led away from using non-enteric coated tablets. Ex.1021(Sands), ¶¶, [0012], [0029]-[0030]; Ex.2041(WO2008/028193). By 2008, no therapeutically effective oral tablet formulation for 5-azacytidine was known. Ex.2087(Grønbæk), 395; Ex.2051(Berkland Decl.), ¶44.

III. THE '628 PATENT

A. The Invention of Orally Administered 5-Azacytidine

1. Enterically-coated formulations

One of the research groups investigating oral 5-azacytidine in the mid-2000s was a company called “Pharmion.” Pharmion successfully developed Vidaza®, and then turned its attention to developing an oral formulation of 5-azacytidine.

Ex.1007(Vidaza® Label 2004), -0005, -0025; Ex.1034(Stoltz); Ex.2040(Ward);
Ex.2123(60/824,320); Ex.2054(Etter Decl.), ¶17.

Given the known chemical and enzymatic instability of 5-azacytidine, researchers at Pharmion believed that the oral formulation would need to be designed to prevent its premature degradation. Ex.2054(Etter Decl.), ¶19. Specifically, Pharmion scientist Dr. Jeffrey Etter (a '628 patent inventor) conducted a study using an *ex vivo* intestinal model that suggested that 5-azacytidine is best absorbed through the colon. *See e.g.*, Ex.2123(60/824,320), ¶¶[00105]-[00108]; Ex.2041(WO2008/028193), ¶¶[00120]-[00128]; Ex.2054(Etter Decl.), ¶¶2, 23. This led Dr. Etter to develop an enterically-coated formulation of 5-azacytidine designed to release in the colon and protect the drug from degradation in the stomach and upper gastrointestinal tract. Ex.2123(60/824,320), ¶¶[0022]-[0023], [00114]; Ex.2041(WO2008/028193), ¶¶[0024]-[0025], [00134]; Ex.2054(Etter Decl.), ¶24. This work on enterically-coated tablets is described in U.S. Provisional Patent Application 60/824,320 and subsequent filings that disclose enterically-coated formulations. *See* Ex.2123(60/824,320); Ex.2124(US2008/0057086), ¶¶[0132], [0137], [0174]; Ex.2041(WO2008/028193); Ex.2054(Etter Decl.), ¶¶23-25.

2. Non-enterically coated formulations

The invention of the non-enterically coated 5-azacytidine compositions and methods of use claimed in the '628 patent occurred serendipitously. Ex.2054(Etter Decl.), ¶¶32. Pharmion conducted a small-scale pilot study and showed absorption of 5-azacytidine following oral administration of an enterically-coated tablet formulation. Ex.2054(Etter Decl.), ¶26. However, Pharmion was unable to repeat that result, instead finding minimal absorption in patients. *See e.g.*, Ex.1050(61/157,875), Figs. 10-15, ¶¶[0039]-[0044], Tables 2-3, 5, ¶¶[00187], [00189]-[00193]; Ex.1051(61/201,145), Tables 2-3; Ex.1001('628 patent), Figs. 10-15, 9:6-25, Tables 3-5, 7, 73:1-74:16; Ex.2054(Etter Decl.), ¶27.

Faced with this inconsistent result, the inventors of the '628 patent investigated the composition of the tablets used in the pilot study. To their surprise, they discovered that the tablet formulation used was manufactured incorrectly, which resulted in a “leaky” coating. Ex.1001('628 patent), 64:19-21; Ex.1051(61/201,145), ¶[0054]; Ex.1050(61/157,875), ¶[00166]; Ex.2054(Etter Decl.), ¶¶8, 28. From that discovery, the inventors considered new ways of administering 5-azacytidine and hypothesized that a therapeutically effective amount of 5-azacytidine could be administered using a non-enteric coated tablet formulation. Ex.2054(Etter Decl.), ¶29.

To test their hypothesis, the inventors developed and evaluated several non-enteric coated tablet formulations of 5-azacytidine. Ex.1051(61/201,145), ¶[0056], Fig. 1, Tables 1-3; Ex.2054(Etter Decl.), ¶¶30-31. That work for the first time showed that a therapeutically effective amount of 5-azacytidine could be administered to patients with a non-enteric coated tablet. Ex.1001('628 patent), 34:30-36, 4:21-27, 57:46-63, 68:47-73:8. The '628 patent describes these non-enterically coated tablet formulations of 5-azacytidine. Ex.1001('628 patent), Tables 3-5, 7, 64:29-50, Fig. 1. The inventors conducted clinical studies and determined that “immediate release azacitidine formulations provide a superior percent exposure... than enteric-coated azacitidine formulations.” Ex.1001('628 patent), 73:3-6; *see also id.*, 74:14-16; Ex.1051(61/201,145), ¶[0070]; Ex.2054(Etter Decl.), ¶31. Thus, despite the known chemical and enzymatic instability of 5-azacytidine, the inventors made the “surprising discovery that 5-azacytidine and related compounds are best absorbed and most efficaciously delivered if instantly released, upon oral administration, in the upper gastrointestinal tract, e.g., the stomach.” Ex.1051(61/201,145), ¶[0022]; Ex.1001('628 patent), 71:39-44, 73:1-6; Ex.2054(Etter Decl.), ¶31-32.

B. Specification

The '628 patent contains background describing 5-azacytidine and its known anti-tumor activity. *See, e.g.*, Ex. 1001('628 patent), 3:28-47. While

acknowledging that oral administration of 5-azacytidine “would be more desirable and convenient for patients and doctors” than administration by injection, the patent recognizes that “oral delivery of cytidine analogs has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor permeability.” *Id.*, 3:48-56. The patent also explains that it was understood in the literature that oral tablet formulations of cytidine analogs—like 5-azacytidine—“have required [an] enteric coating of the drug core” to protect against “hydrolysis in the stomach” and to ensure that the drug reaches “specific regions of the lower gastrointestinal tract” where it is “preferably absorbed....” *Id.*, 3:57-4:7.

Against this background, the '628 patent explains the inventors' unexpected discovery that 5-azacytidine can be orally administered as a non-enterically coated tablet. Ex. 1001('628 patent), 64:10-50, Tables 3-5, 7; *see also* Ex.1051(61/201,145), ¶[0022]. The specification discloses manufacturing 5-azacytidine non-enteric coated tablets using direct tablet compression. Ex.1001('628 patent), Tables 3-5, 7, Figure 1, 64:11-53. In Example 1, the hydroxypropyl cellulose film coating was dispersed using organic solvents, consistent with limiting 5-azacytidine's exposure to water. *Id.*, 64:47-49. Example 2 describes additional studies that showed aqueous film coatings did not have a significant effect on hydrolytic degradation of 5-azacytidine. *Id.*, 67:31-38, Table 6. The specification reports pharmacokinetic, and efficacy data following the oral

administration of these non-enterically coated tablet formulations. Ex.1001('628 patent), 67:61-74:62, Tables 3-5, 7.

C. Prosecution History

U.S. Patent Application 12/466,213 (the "'213 application") underwent substantive examination at the Patent Office before being properly granted as the '628 patent.

During prosecution, the Applicant overcame multiple rejections by establishing that a tablet without an enteric coating was novel and unique. Ex.1022, 0651-0653, 0714-0733, 1079-1082, 1107-1121, 2020-2024, 2063-2084. The Applicant supported its arguments with a declaration by Dr. Charles L. Beach. Ex.1022(Beach Decl.), 2086, 2069, 2078-2079. Dr. Beach explained that at the time of the application, 5-azacytidine was only approved for intravenous or subcutaneous administration and that there was a strong prejudice in the art against developing an immediate release, non-enteric coated tablet formulation of 5-azacytidine due to its chemical and enzymatic instability and poor permeability. *Id.*, 2087-2089, 2073. Dr. Beach supported his declaration with post-filing data and data present in the application demonstrating that the claimed 5-azacytidine non-enteric coated tablets exhibit unexpected pharmacokinetic, pharmacodynamic, and clinical properties. *Id.*, 2079-2084, 2090-2092.

On May 28, 2014, the Examiner issued a notice of allowance. Ex.1022, 2133-2140. Pointing to Dr. Beach's declaration, the Examiner concluded that the prior art rejections were inappropriate in view of the detailed analysis of the art presented. Ex.1022, 2138. The Examiner also noted that the "surprisingly high anti-neoplastic medicinal activities of the claimed non-enteric coated pharmaceutical composition, has been identified as unexpected." *Id.*

D. Challenged Claims

The '628 patent's claims reflect the inventors' discovery that a therapeutically effective amount of 5-azacytidine can be orally administered using non-enterically coated tablets. Claims 1 and 28 are independent claims reciting a pharmaceutical composition and a method of treatment, respectively. The dependent claims add limitations relating to excipients, the absence of a cytidine deaminase inhibitor, dosage amounts, pharmacokinetic parameters, types of coatings, film coatings, and single unit dosage forms. Ex.1001('628 patent), claims 2, 6-9, 11-27, 32-36, 38-43.

E. Onureg®

The invention of the '628 patent led to the development of the first FDA-approved orally administered formulation of 5-azacytidine, Onureg®. Ex.2055(FDA Approves Onureg®); Ex.2062(Onureg® Label); Ex.2103(Oral CC-486); Ex.2053(Blum Decl.), ¶15. Onureg® was approved in 2020 for "continued

treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.” Ex.2062(Onureg® Label); Ex.2053(Blum Decl.), ¶16.

IV. PERSON OF ORDINARY SKILL IN THE ART

A POSA relating to the subject matter of the '628 patent would have had (1) a Pharm.D., and/or a Ph.D. in pharmaceutical sciences, biomolecular engineering, chemical engineering, chemistry, or related discipline or an M.D.; and (2), at least two years of experience with oncology, medicine, pharmaceutical design, or formulation of oral dosage forms.

V. CLAIM CONSTRUCTION

A. “Non-Enteric Coated”

In related district court litigation, the court adopted Patent Owner's construction of “non-enteric coated” as a formulation “that does not comprise a coating intended to release the active ingredient(s) beyond the stomach.”

Ex.2032(*Celgene v. Accord* 1:21-cv-01795-RGA Doc 40), 1. This definition is provided in the '628 patent. Ex.1001('628 patent), 11:42-45. Petitioner does not dispute this construction. Pet., 20. The Board preliminarily agreed. DI, 14.

B. “Test Subject”

In related district court litigation, Patent Owner agreed to construe the term “test subject” as “a human or other animal who received the recited pharmaceutical composition in connection with a test of the recited parameter.” Ex.2045(*Celgene v. Accord* 1:21-cv-01795-RGA Doc 35), 3. Petitioner does not dispute this construction. Pet., 20. The Board preliminarily agreed. DI, 16.

C. Claims 14 and 15

Claim 13 depends from claim 1 and recites “wherein the tablet further comprises a sugar coating, a film coating, or a compression coating.” Ex.1001('628 patent), claim 13. Claim 14 depends from claim 13 and recites “wherein the film coating is a cellulose ether polymer.” Claim 15 depends from claim 14 and further limits the cellulose ether polymer to specific species.

Claims 14 and 15 are limited to compositions with a “film coating.” This is clear from tracing the limitation through the claim dependencies. Claim 13 recites three types of coatings, listing them with disjunctive word “or,” not the conjunctive word “and.” Claim 14 recites “the film coating” of claim 13 and further specifies a type of film coating—cellulose ether polymer—and is clearly directed to the “film coating” alternative of the coated tablet recited in claim 13 and not to all three species in claim 13 (two of which are not film coatings). Claim 15 further specifies types of “the cellulose ether polymer” coating of claim 14, which again is

clearly directed to the “film coating” alternative. Accordingly, the positive recitation of “the film coating” and “the cellulose ether polymer” in claims 14 and 15 limits the claims to these features. This interpretation is also supported by the specification, which describes film-coated tablets with a cellulose ether polymer as an embodiment of the tablets. Ex.1001('628 patent), 40:53-41:34.

Petitioner's proposed construction (*see* Pet., 25-26) that claims 14 and 15 do not limit the scope of claim 13 to the recited film coating species is nonsensical. For example, under Petitioner's construction, a sugar-coated tablet without a film-coating is still within the scope of claims 14 and 15 although it does not contain the film coating elements positively recited in those claims. Petitioner's proposed construction should be rejected as inconsistent with the claim language.

VI. THE ASSERTED REFERENCES

A. Ionescu (Ex.1004)

Ionescu is a PCT Application, filed on March 16, 2004, by Pharmion and Ash Stevens Inc, and published on September 30, 2004. Ex.1004(Ionescu).

Ionescu is the primary reference underlying Grounds 1-3.

Ionescu relates to the “isolation [and characterization] of crystalline polymorphic and pseudopolymorphic forms of 5-azacytidine....”

Ex.1004(Ionescu), 1:8-10, 2:7-9; Ex.2051(Berkland Decl.), ¶61. Ionescu discloses that different crystal or pseudocrystal structures “may affect, for example, the

solubility [and] stability” of active pharmaceutical ingredients, such as 5-azacytidine. Ex.1004(Ionescu), 1:22-25, 1:28-31. Ionescu provides X-ray powder diffraction patterns for eight different 5-azacytidine crystalline forms and methods for synthesizing several of them. Ex.1004(Ionescu), 2:11-14, 2:23-26, 3:7-12:10, 15:5-22:26; Figs. 1-8; Ex.2051(Berkland Decl.), ¶61.

Ionescu notes that 5-azacytidine may be used in treating diseases such as MDS (Ex.1004(Ionescu), 1:10-11; Ex.2051(Berkland Decl.), ¶62) and provides a general disclosure that the forms of 5-azacytidine may be used in a pharmaceutical composition. Ex.1004(Ionescu), 2:26-28; Ex.2051(Berkland Decl.), ¶62. Ionescu then discloses a generic list of different types of pharmaceutical formulations. Ex.1004(Ionescu), 12:11-14:29; Ex.2051(Berkland Decl.), ¶62. Ionescu separately notes, without referring to any particular embodiment or formulation and without further guidance, that “[t]he compositions of the invention can be formulated so as to provide quick, sustained, controlled, or delayed release of the drug substance after administration to the patient by employing procedures well known in the art.” Ex.1004(Ionescu), 13:7-10; Ex.2051(Berkland Decl.), ¶62.

The only working example in Ionescu is an injectable slurry of 5-azacytidine. Ex.1004(Ionescu), 2:16-18, 6:15-20, 9:11-16, 21:23-22:6; Ex.2052(Berkland Decl.), ¶63. Ionescu discloses no working examples or data for an oral formulation of 5-azacytidine. Ex.2051(Berkland Decl.), ¶63. Ionescu also

does not address the known chemical and enzymatic instability issues with orally administering 5-azacytidine, let alone purport to solve them. Ex.2051(Berkland Decl.), ¶63.

B. Atadja (Ex.1005)

Atadja is a PCT Application, filed on May 19, 2004, by Novartis and published on December 2, 2004. Ex.1005(Atadja). Atadja discloses combinations of chemotherapeutic agents and histone deacetylase inhibitors (HDAs) for treating proliferative diseases and describes the HDAs and their structures. Ex.1005-0001(Atadja), Abstract; -0010-0023, 9:15-22:5; Ex.2051(Berkland Decl.), ¶64.

Atadja also discloses that ““chemotherapeutic agent(s)’ is [] broad” and includes a list of over 130 compounds. Ex.1005(Atadja), 2:23, 3:1-24, 3:25-9:14; Ex.2051(Berkland Decl.), ¶64.

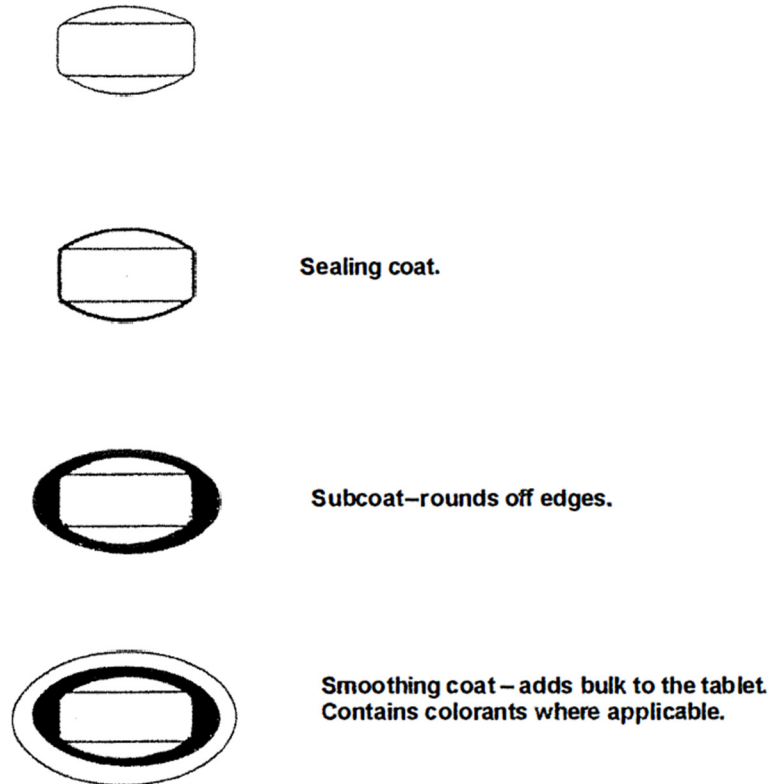
Atadja identifies 5-azacytidine as one possible chemotherapeutic option out of the long list for administration with a HDAI. *See, e.g.*, Ex.1005-0027-0028(Atadja), 26:28-27:16; Ex.2051(Berkland Decl.), ¶64. For the chemotherapeutic agents, Atadja states that “[p]referably, the compounds or the pharmaceutically acceptable salts thereof, are administered as an oral pharmaceutical formulation in the form of a tablet, capsule or syrup; or as parenteral injections if appropriate.” Ex.1005-0028(Atadja), 27:16-18; Ex.2051(Berkland Decl.), ¶65.

Atadja does not contain any working examples of formulations of 5-azacytidine. Ex.1005(Atadja), 27-33. Nor does Atadja address the known instability issues with orally administering 5-azacytidine, let alone purport to solve them. Ex.2051(Berkland Decl.), ¶66.

C. Gibson (Ex.1006)

Gibson is a general reference textbook and is “intended to be a practical guide to pharmaceutical preformulation and formulation” that “can be used as a reference source and a guidance tool for those working in the pharmaceutical industry or related industries....” Ex.2063(Gibson Supplemental), 1; Ex.2051(Berkland Decl.), ¶67. Gibson discloses that “[s]pecial considerations and issues for the formulation development for each route [of administration] and type of dosage form are discussed....” Ex.2063(Gibson Supplemental), 11; Ex.2051(Berkland Decl.), ¶67. Gibson describes that oral solid dosage forms may be sugar-coated through a “multistep process” typically employing a seal coat, a subcoat, and a smoothing coat (Ex.1006-0062(Gibson); Ex.2051(Berkland Decl.), ¶67) as depicted in Figure 11.24 reproduced below.

Figure 11.24 Stages of sugar coating.



Ex.1006-0063(Gibson).

Gibson explains, “One of the reasons for [sugar] coating tablets is to protect the drug substance from environmental factors such as moisture,” and the sealing coat ensures that coating solutions do not penetrate into the core. Ex.1006-0063(Gibson); Ex.2051(Berkland Decl.), ¶68. Gibson discloses both enteric coated and non-enteric coated tablets (*see, e.g.*, Ex.1006-0068(Gibson); Ex.2051(Berkland Decl.), ¶68), and explains that sugar-coated tablets may be used with an enteric coating. Ex.1006-0070(Gibson) (“The original enteric coating material [shellac], originally used in sugar-coated tablets.”); Ex.2051(Berkland

Decl.), ¶68. Gibson also states, “The most common type of modified release coating is the enteric coat that is designed to prevent release of the drug substance in the stomach because the drug is either irritant to the gastric mucosa or it is *unstable in gastric juice*.” Ex.1006-0068(Gibson), 439; Ex.2051(Berkland Decl.), ¶68. Gibson does not mention 5-azacytidine or any treatment of MDS or AML. Ex.2054(Berkland Decl.), ¶68.

D. Pharmion-PR (Ex.1010)

Pharmion-PR is a press release that is dated June 2, 2007. Ex.1010-0005(Pharmion-PR). Pharmion-PR provides high level results of a pilot study designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered 5-azacytidine in patients with MDS, AML, or solid tumors. Ex.1010-0005(Pharmion-PR); Ex.2051(Berkland Decl.), ¶69. Pharmion-PR discloses that an 80mg dose given to three patients resulted in an oral bioavailability of 18% relative to the bioavailability of subcutaneous Vidaza®. Ex.1010-0005(Pharmion-PR); Ex.2051(Berkland Decl.), ¶69. Pharmion-PR discloses a subsequent multi-dose escalating study of oral 5-azacytidine was being performed. Ex.1010-0005(Pharmion-PR); Ex.2051(Berkland Decl.), ¶69.

Pharmion-PR does not disclose the oral formulation of 5-azacytidine employed in either study, let alone specify that a non-enterically coated tablet was used. Ex.2051(Berkland Decl.), ¶69.

VII. THE '628 PATENT CLAIMS ARE NOT ANTICIPATED BY IONESCU (GROUND 1)

A. Petitioner Has Failed to Show That Ionescu Discloses a Non-Enteric Coated Tablet as Required by All Challenged Claims

Each of the challenged claims requires a “non-enteric coated tablet” for providing a therapeutically effective amount of 5-azacytidine. As explained below, the Petition does not establish that Ionescu discloses “a non-enteric-coated tablet,” and Ground 1 fails. Ex.2051(Berkland Decl.), ¶¶75-84.

1. Ionescu's “sugar-coated” tablets do not disclose a “non-enteric coated tablet”

As the Board recognized in its Institution Decision, the Petition relies exclusively on Ionescu's disclosure of a “sugar-coated” tablet for purposes of the “non-enteric coated” tablet limitation of the challenged claims. Paper 7(DOI), 34; *see* Pet., 22 (“At least the sugar-coated tablets of Ionescu are NEC....”). But Petitioner's anticipation theory only works if *all* sugar-coated tablets are necessarily non-enteric coated, such that the “non-enteric coated” limitation is inherent in the disclosure of a sugar coating. The Petition does not establish inherency for this limitation, and Petitioner's anticipation theory is contradicted by the prior art teachings. Ex.2051(Berkland Decl.), ¶¶75-84.

As the '628 patent makes clear, a “non-enteric coated tablet” is a tablet “that does not comprise a coating intended to release the active ingredient(s) beyond the stomach.” Ex.1001('628 patent), 11:42-45. Sugar coatings are used to produce an

“[e]legant final product,” “for identification purposes,” and to provide “protection from [the] environment.” Ex.1006(Gibson), 0072; Ex.2051(Berkland Decl.), ¶78.

A sugar coating is not synonymous with a non-enteric coating; in fact, Petitioner's own cited references disclose enterically coated tablets with a sugar coating.

Ex.1006(Gibson), 0062, 0063, 0070, 0072; Ex.1030(Remington), 0009, 0047, 0049-0050; Ex.2051(Berkland Decl.), ¶¶79-82; *see also* Ex.2020(Lieberman), 79-80, 83; Ex.2028(Remington 2005), 930-931. Therefore, as the Board recognized in its Institution Decision (Paper 7(DOI), 36-39), the presence or absence of a sugar coating alone does not disclose the tablet's release profile nor indicate whether the tablet is enterically coated. Ex.2051(Berkland Decl.), ¶¶79-83.

That is dispositive of Petitioner's anticipation theory. In Ground 1, Petitioner relies solely on the “sugar-coated tablets of Ionescu” as satisfying the non-enteric coated tablet limitation (Pet., 22-23), and the Board's review is limited to the prior art disclosures expressly identified in the Petition for each limitation.¹

EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc., 859 F.3d 1341, 1349-

¹ Petitioner makes *no* argument that an uncoated tablet is disclosed by Ionescu and would be used. Their expert Dr. Graham Buckton admits that uncoated tablets would be “unusual” as of 2008 and that coated tablets “were most preferred.” Ex.1002(Buckton Decl.), ¶46, ¶124.

1350 (Fed. Cir. 2017). Because the “sugar-coated tablets of Ionescu” do not disclose the “non-enteric coated tablet” limitation of each challenged claim, the Board should reject the anticipation challenge in Ground 1.

2. A POSA in December 2008 would not have understood that sugar-coated tablets of 5-azacytidine would have been non-enterically coated

Petitioner's reliance on Ionescu's disclosure of sugar-coated tablets also fails because it is inconsistent with the understanding of a POSA. “[T]he dispositive question regarding anticipation [i]s whether *one skilled in the art* would reasonably understand or infer from the [prior art reference's] teaching' that every claim element was disclosed in that single reference.” *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (emphasis in original) (internal citations omitted). Further, “[a]mbiguous references do not anticipate a claim” as “a single reference” is required to “describe the claimed invention *with sufficient precision and detail* to establish that the subject matter existed in the prior art.” *Wasica Fin. GmbH v. Cont'l Auto. Sys.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017) (emphasis in original) (citing *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002)).

To the extent a POSA understood Ionescu to disclose an oral, coated tablet of 5-azacytidine, the POSA would also have understood the formulation to be an enterically coated tablet to avoid the stomach's acidic environment and reduce

hydrolysis, and to avoid enzymatic degradation in the stomach—not the non-enteric tablet of the claims. Ex.2051(Berkland Decl.), ¶85. Petitioner cannot demonstrate that a POSA would have understood sugar-coated tablets to disclose non-enteric coated tablets in view of 5-azacytidine's known stability problems. *See* Sections VIII.A-VIII.B.

B. Ionescu Fails to Disclose a Film Coated Tablet as Required by Claims 14 and 15

Under a proper construction, claims 14 and 15 require a film coating. *See* Section V.C. Yet Petitioner and its expert Dr. Buckton have not pointed to any disclosure in Ionescu of a film coating, much less the film coatings recited in claims 14 and 15. *See* Pet., 25-26; Ex.1002(Buckton Decl.), ¶¶94-98. Nor could they make such a showing because Ionescu is entirely silent on film coatings. Ex.1004(Ionescu); Ex.2051(Berkland Decl.), ¶86; Ex.2050(Buckton Tr.), 81:8-19. Therefore, Petitioner's anticipation challenge to claims 14 and 15 fails.

C. Ionescu Does Not Inherently Anticipate the Pharmacokinetic Values Required by Claims 11, 18, 20-22, 38, 40, 42, and 43

Dependent claims 11, 18, 20-22, 38, 40, 42, and 43 require that the claimed compositions or methods achieve certain specified pharmacokinetic parameters: (1) a minimum area-under-the-curve (AUC); (2) a maximum plasma concentration ($C_{\max}$); or (3) a time to a maximum plasma concentration ($T_{\max}$). Ex.2052(Grass Decl.), ¶¶27-30. Ionescu, however, does not provide any pharmacokinetic values,

much less those recited in the challenged claims. Ex.2050(Buckton Tr.), 71:6-72:19, 73:19-74:2, 67:1-9; Ex.2052(Grass Decl.), ¶¶35, 40, 46.

Petitioner argues that these values are inherently anticipated because they are the natural results of administering a prior art formulation. Pet., 29. But pharmacokinetic values are dose- and formulation-dependent (*see, e.g.*, Ex.1001('628 patent), Fig. 12), and Petitioner has not identified the alleged tablet formulation disclosed in the prior art, let alone offered proof of how it compares with the compositions disclosed in the '628 patent that produced the claimed pharmacokinetic parameters. Pet., 29; Ex.2051(Berkland Decl.), ¶¶50, 62; Ex.2052(Grass Decl.), ¶¶41, 47-48.

Petitioner relies upon Dr. Hannah Batchelor's modeling, but her analysis is unreliable (*see* Section VIII.E.2) and does not show that the claimed pharmacokinetic parameters are inherent in Ionescu. Indeed, Dr. Batchelor did not even review Ionescu, let alone design her model based on any formulation disclosed in Ionescu. Ex.1003(Batchelor Decl.) (failing to cite to Ionescu, Atadja, Gibson, or Pharmion-PR); Ex.2049(Batchelor Tr.), 126:5-12 ("I haven't considered formulation attributes particularly within this, other than immediate release."); Ex.2050(Buckton Tr.), 108:19-109:11. Moreover, Dr. Batchelor failed to consider factors such as excipients and other properties that would affect the composition's pharmacokinetic profile. Ex.2049(Batchelor Tr.), 126:5-12; *see*

also Ex.2050(Buckton Tr.), 108:19-109:11; Ex.2067(Aulton), 162. Her modeling falls well short of the exacting standard required for showing inherent anticipation. Ex.2052(Grass Decl.), ¶¶42, 49-74.

Because Petitioner has not identified any formulation disclosed in Ionescu with the claimed pharmacokinetic parameters, Petitioner's anticipation challenge fails. Ex.2052(Grass Decl.), ¶¶39, 76, 98.

D. Ionescu Is Not Enabling

Ground 1 fails for the additional reason that Ionescu does not enable a POSA to practice the embodiment relied upon as anticipatory in the Petition without undue experimentation. *See Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Rsch.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003) ("To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate," which "requires that 'the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.'" (citations omitted)). The eight factors under *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), provide the legal standard for evaluating whether the degree of experimentation is undue.

The *Wands* factors confirm that Ionescu does not enable a therapeutically effective amount of 5-azacytidine in a sugar-coated, non-enteric coated tablet. Ex.2051(Berkland Decl.), ¶¶87-94. The relative skill level of those in the art is

discussed above and is relatively high (Factor 1). *See* Section IV. The breadth of the claims and nature of the invention are described above (Factors 2-3). *See* Section III. A POSA would need to experiment given the known instability of 5-azacytidine (Factor 4). *See* Sections II.C-II.D. Ionescu does not disclose and provides no guidance on making or using a sugar-coated, non-enteric coated tablet with a therapeutically effective amount of 5-azacytidine (Factor 5) and contains no working examples of any oral 5-azacytidine formulations, much less a non-enteric coated tablet (Factor 6). Ex.2051(Berkland Decl.), ¶92; Ex.2050(Buckton Tr.), 72:3-9, 71:6-72:2, 73:19-74:2, 72:10-19, 67:1-9; 66:6-22, 64:16-22; Section VI.A. Indeed, Ionescu only discloses working examples of the preparation of 5-azacytidine suspended in a water-based solution, *i.e.*, “slurries,” for subcutaneous injection. *See* Ex.1004(Ionescu), 2:16-18, 6:15-20, 9:11-16, 21:23-22:6; Section VI.A. Ionescu also contains no *in vivo* studies disclosing a sugar-coated, non-enteric coated tablet with a therapeutically effective amount of 5-azacytidine to treat MDS or AML. *See* Ex.2053(Blum Decl.), ¶¶25-26, 31. The state of the prior art was complex, unpredictable, and counseled against non-enteric coated tablet formulations of oral 5-azacytidine (Factors 7-8). *See* Sections II.C-II.D; Ex.2051(Berkland Decl.), ¶93. Research into 5-azacytidine as a cancer therapeutic began nearly 40 years prior to Ionescu. During that time, development of a 5-azacytidine had proven to be complex and faced numerous challenges. *See, e.g.*,

Ex.2041(WO2008/028193), ¶[0005], ¶[0007]. As previously discussed (*see* Sections II.C-II.D), the state of the art established that it would be unpredictable for a non-enteric, orally administered tablet of 5-azacytidine to be therapeutically effective. *See, e.g., id.* In fact, the prior art explicitly suggested that any oral formulation of 5-azacytidine would require protection from the harsh, gastric environment, *i.e.*, an enteric coat. *See, e.g.,* Ex.2123(60/824,320). Ionescu does not address any of the known issues with the oral administration of 5-azacytidine, let alone identify a solution.

In short, Ionescu's boilerplate description of potential formulation techniques is no different from formulation textbook disclosures—for example, Remington. *See* Section VIII.A.4 But that generic disclosure was insufficient to enable a POSA to develop a therapeutically effective, non-enteric coated tablet of 5-azacytidine. And that failure was not for lack of trying, as the dozens of references discussing these efforts confirm. *See* Sections II.C-II.D.

In view of the foregoing, a POSA would have needed to engage in undue experimentation from the boilerplate disclosures of Ionescu, especially in view of the complex and unpredictable nature and state of the art as of December 2008. Ex.2054(Berkland Decl.), ¶94. Accordingly, because Ionescu does not enable a therapeutically effective amount of 5-azacytidine in a sugar-coated, non-enteric coated tablet, Ionescu does not anticipate the claims challenged in Ground 1.

VIII. THE '628 PATENT CLAIMS WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF IONESCU IN COMBINATION WITH ATADJA AND GIBSON AND THE KNOWLEDGE OF A POSA (GROUND 2)

Petitioner fails to establish that Ionescu, Atadja, and Gibson in view of the knowledge of a POSA would have rendered obvious “a non-enteric-coated tablet” as recited in the challenged claims. Ex.2051(Berkland Decl.), ¶95.

A. A POSA Would Not Have Been Motivated to Pursue and Select an Oral, Non-Enteric Coated Tablet of 5-Azacytidine

1. Petitioner's theory that a POSA would have selected a non-enteric coated tablet from Ionescu's disclosure is flawed for the same reasons as its anticipation challenge

Petitioner's obviousness challenge in Ground 2 suffers from the same defect as its anticipation challenge in Ground 1. As with Ground 1, Petitioner's obviousness challenge rests on the premise that Ionescu discloses a non-enteric coated tablet of 5-azacytidine that a POSA either (i) would have been motivated to select; or (ii) that would have been obvious to try. *See* Pet., 32-38. However, the portions of Ionescu underlying the Petition do not disclose non-enteric coated tablets; they disclose “sugar-coated” tablets (which are not synonymous).² *See* Section VII.A. Because a non-enteric coated tablet is not disclosed by Ionescu's

² As noted above, Petitioner makes *no* argument that an uncoated tablet is disclosed by Ionescu and would be used. *See* Section VII.A, fn. 1; Ex.1002(Buckton Decl.), ¶46, ¶124.

“sugar-coated” tablet, a POSA could not “select” (Pet., 36) a non-enteric coated tablet from that disclosure in Ionescu. Similarly, a non-enteric coated tablet is not among the “limited number of oral dosage forms disclosed in Ionescu” (Pet., 38) that would have been obvious to try because a non-enteric coated tablet is not disclosed by Ionescu’s “sugar-coated” tablet.

Petitioner did not disclose any obviousness theory based upon *making* a non-enteric coated tablet in view of the prior art disclosures; its obviousness challenge rests exclusively on the notion that a POSA would have *selected* a non-enteric coated tablet from Ionescu’s disclosure. *See, e.g.*, Pet., 32 (“[A] POSA, when *selecting* the dosage form of 5-azacytidine from among those disclosed by Ionescu....”); Pet., 36 (Heading V.B.1.a.ii: “A POSA Would Have Been Motivated to Pursue and *Select* a NEC Tablet of 5-Azacytidine From the Oral Dosage Forms of Ionescu”). Petitioner framed its obviousness challenge as a selection from the same disclosure in Ionescu underlying its anticipation challenge in Ground 1. As a result, Petitioner’s obviousness challenge in Ground 2 fails for the same reasons addressed in Ground 1.

2. Petitioner has not shown that a POSA would select a non-enteric coated tablet as the “default” choice for 5-azacytidine

Lacking any prior art disclosure of any actual working example of a non-enteric coated tablet of 5-azacytidine, Petitioner instead asserts that it would have

been obvious to select a non-enterically coated tablet formulation for 5-azacytidine because non-enteric coatings are the “default” choice. *See, e.g.,* Pet., 36. But that argument fails to account for the state of the art at the time of the invention. If Petitioner were right that the claimed invention was truly the “default,” the decades of failure that preceded the invention of the '628 patent would have been avoided. *See* Sections II.C-II.D; Ex.2051(Berkland Decl.), ¶¶96-113. Petitioner's assertions about what the “default” would have for 5-azacytidine are incorrect for several reasons.

a. Petitioner's obviousness theory cannot be reconciled with the known instability of 5-azacytidine

Any obviousness analysis must account for the well-known challenges with the oral administration of 5-azacytidine, including its susceptibility to hydrolysis and enzymatic degradation. *See* Sections II.C-II.D; Ex.2051(Berkland Decl.), ¶¶96-97. Moreover, the prior art disclosed that 5-azacytidine could be absorbed through the lower intestines. Ex.2041(WO2008/028193), ¶¶[0024]-[0025], [00120]-[00123]. Those factors are inconsistent with the use of non-enteric coated tablets, and Petitioner tellingly has cited *no* evidence of any prior art use of non-enteric coated tablets of 5-azacytidine. Ex.2051(Berkland Decl.), ¶96. Indeed, Gibson, relied upon by Petitioner, makes clear that enteric coatings are used in situations where “the drug... is unstable in gastric juice” (Ex.1006(Gibson), 0068), which is precisely what the prior art disclosed about 5-azacytidine. *See* Sections

II.C-II.D; Ex.2051(Berkland Decl.), ¶¶96. And consistent with the state of the art, even the inventors of the '628 patent initially pursued an enterically-coated tablet formulation of 5-azacytidine and only changed course when they encountered a problem that led them to develop non-enteric coated tablet formulations, contrary to the guidance provided in the literature at that time. Ex.2054(Etter Decl.), ¶¶27-30; *see* Section III.A.

Petitioner's experts Drs. Buckton and Batchelor acknowledge the known hydrolytic stability problems with 5-azacytidine. *See* Ex.1002(Buckton Decl.), ¶¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46. But they do not attempt to reconcile their opinions with 5-azacytidine's known instability and ignore the enzymatic degradation of 5-azacytidine. Ex.2050(Buckton Tr.), 47:20-48:14, 56:18-57:7. Their conclusion that non-enterically coated tablets would be the "default" choice is not grounded in any facts relating to 5-azacytidine.

Ex.2051(Berkland Decl.), ¶¶96-97. Indeed, Dr. Buckton admitted that he has no experience with 5-azacytidine. Ex.2050(Buckton Tr.), 9:7-10:18. Nor did he consult with a clinician or person with 5-azacytidine experience despite admitting that a POSA would work in collaboration with others with this type of experience. Ex.1002(Buckton Decl.), ¶¶17, 116; Ex.2050(Buckton Tr.), 16:12-16. To the extent Dr. Buckton relies on Dr. Batchelor's modeling as providing a motivation to select a non-enteric coated tablet, that argument is not in the Petition, Dr. Batchelor

has no experience with 5-azacytidine (Ex.2049(Batchelor Tr.), 22:2-23:7) and her unreliable modeling does not account for numerous parameters including the level of degradation in the stomach. *See* Section VIII.E.2; Ex.2052(Grass Decl.), ¶¶53-67, 75; Pet., 33; Ex.1002(Buckton Decl.), ¶119.

Petitioner's generic assertions about what the "default" would have been misses the point. What matters for purposes of assessing obviousness is not what a POSA would have done in the abstract, but rather what a POSA would have done in view of the prior art teachings about the compound at issue. *See Daiichi Sankyo Co. v. Matrix Lab, Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (determining obviousness depends on "knowledge in the art of the functional properties and limitations of the prior art compounds" (emphasis added) (citations omitted)); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). The Petition does not address that critical question, and Petitioner therefore cannot carry its burden of showing that the challenged claims would have been obvious.

- b. There was no prior art disclosure of the use of non-enterically coated 5-azacytidine tablet*
 - (1) Pharmion-PR does not disclose a non-enteric coated tablet

Petitioner asserts that "no compelling reason existed to deviate from the default preference for NEC" alleging that "a POSA would have understood that a NEC formulation of 5-azacytidine was orally bioavailable and well tolerated." Pet.,

37 (referencing Section IV.A.3). However, the only evidence that Petitioner cites in Section IV.A.3 to support this position is Pharmion-PR's (Ex.1010) disclosure that orally administered 5-azacytidine is bioavailable. Pet., 12. The Pharmion-PR does not disclose **any** details on the type of oral formulation used.

Ex.2050(Buckton Tr.), 90:10-19.³ Petitioner cannot rely on Pharmion-PR as disclosing that a tablet, let alone a non-enteric tablet, was orally bioavailable and well tolerated because Pharmion-PR **only** discloses that some undescribed oral formulation was 18% bioavailable in humans relative to the bioavailability of subcutaneous administration of Vidaza®. Ex.1010(Pharmion-PR);

Ex.2051(Berkland Decl.), ¶99. Because Pharmion-PR does not disclose how the 5-azacytidine was formulated, it does not provide a motivation to use the non-enteric coated tablet formulation claimed in the '628 patent.

In fact, if a POSA were to make any inference from Pharmion-PR, it would be that an **enteric**-coated tablet was used. Ex.2051(Berkland Decl.), ¶100.

³ Although Petitioner does not cite Dr. Buckton's declaration for support, to the extent Dr. Buckton opines on a POSA's understanding that oral 5-azacytidine was bioavailable via administration of a non-enteric coated tablet, his statements are conclusory and based on the same deficient disclosures. See Ex.1002(Buckton Decl.), ¶¶127, 49.

Pharmion-PR is from June 2007, and discusses a “pilot study” “designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered Azacitidine in patients with [MDS], [AML], or other solid tumors.” Ex.1010-0005(Pharmion-PR). WO2008/028193, also from Pharmion, was filed in September 2007 and published in March 2008 and uses similar language to Pharmion-PR to describe a clinical study performed using an *enteric*-coated tablet (see Example 3). Ex.2041(WO2008/028193), ¶¶[00142], [00129]-[00134]. Like Pharmion-PR, WO2008/028193 discloses that an 80mg dose had 18% bioavailability compared to subcutaneous administered Vidaza®. *Id.*, ¶¶[00142], [00157]-[00159].

Accordingly, contrary to Petitioner's assertions, Pharmion-PR is silent on the issue of a non-enteric coated 5-azacytidine tablet and does not teach such a formulation was orally bioavailable. Instead, a POSA as of December 2008 would have understood that contemporaneous Pharmion disclosures (*e.g.*, WO2008/028193) exclusively disclosed *enteric*-coated oral formulations and thus would have understood that Pharmion-PR refers to an enterically coated tablet as well. Ex.2051(Berkland Decl.), ¶100.

- (2) The other references cited in the Petition do not disclose a non-enteric coated tablet formulation

In discussing obviousness, the Board in its Institution Decision also pointed to several references as supporting Petitioner's position that Ionescu teaches a

“sugar coated” tablet that is also a non-enteric coated tablet. Paper 7(DOI), 46-47.

None of these references—Vorbruggen, Sands, Dover, Stoltz, or Ward—discloses a therapeutically effective, non-enteric coated tablet nor would they have motivated a POSA to use a non-enteric coated tablet of 5-azacytidine. For example, Sands (and WO2008/028193) specifically states that an *enteric*-coated tablet formulation should be used. Ex.1021(Sands), ¶¶[0029]-[0030]. Vorbruggen is directed to the class of azapyrimidines and does not suggest that its general disclosure of oral administration applies to 5-azacytidine. Ex.1016(Vorbruggen), Abstract, 4:53-59. Dover reports that oral 5-azacytidine administered alone had no effect. Ex.1031(Dover), 528. And Ward does not disclose the formulation used. Ex.2040(Ward). Thus, none of these references would have altered the prevailing understanding that an enteric coating was necessary to address 5-azacytidine's known instability. Ex.2051(Berkland Decl.), ¶¶101-104. And if anything, the teachings of references like Sands would have reinforced the need to use an enteric coating. Ex.1021(Sands), ¶¶[0029]-[0030].

With respect to Stoltz, the Petition cites Pharmion's 2006 dog studies of oral 5-azacytidine to argue that non-enteric coated formulations would have been the default. *See* Pet., 12 (citing Ex.1034(Stoltz)). But Stoltz does not disclose that the formulation used was non-enterically coated tablets. Ex.1034(Stoltz); Ex.2051(Berkland Decl.), ¶103. Any reliance on Stoltz's disclosure of a 15-minute

T_{max} in a dog study to suggest that there would be no reason to formulate an enteric coated tablet is misplaced because this T_{max} does not disclose that any particular formulation was used. Ex.2050(Buckton Tr.), 44:16-45:13; Ex.2052(Grass Decl.), ¶¶22, 66. And it is not possible to draw reliable conclusions on bioavailability in humans from dog studies because dogs (unlike humans) do not express appreciable levels of the enzyme cytidine deaminase, which was known to cause degradation. Ex.2143(Hirayama), 153; Ex.2051(Berkland Decl.), ¶103. A POSA would not draw conclusions on 5-azacytidine absorption or bioavailability in humans from Stoltz. Ex.1034(Stoltz); Ex.2051(Berkland Decl.), ¶¶103-104.

Indeed, to the extent Stoltz provides any teaching on how to formulate 5-azacytidine, Stoltz would lead a POSA to use an enteric coating. For example, Stoltz emphasizes that 5-azacytidine “must be formulated to avoid the chemical and enzymatic degradation occurring presystemically” (Ex.1034(Stoltz))—which, if anything, would suggest the use of enterically-coated tablets. Ex.2051(Berkland Decl.), ¶103. Moreover, the Pharmion authors state that the oral dosage form will progress into additional clinical evaluation, which a POSA in 2008 would understand to be the 2007-2008 studies described by Pharmion as using enteric coated tablets. Ex.2041(WO2008/028193), ¶¶[00142], [00129]-[00134]; Ex.1010(Pharmion-PR); Ex.2054(Berkland Decl.), ¶103.

Thus, Petitioner has cited no evidence that a POSA would have understood a non-enteric coated formulation was orally bioavailable and well tolerated.

Ex.2051(Berkland Decl.), ¶104.

3. Disclosures of “liquid formulations” would not have assuaged a POSA’s concerns over 5-azacytidine’s stability

Petitioner’s remaining argument for selecting a non-enteric coated tablet is that Ionescu and Atadja teach that 5-azacytidine could be administered as a “liquid syrup” which is incompatible with enteric coatings. Pet., 37. The Board found in the Institution Decision that those in the field were developing oral 5-azacytidine “both with and without enteric coatings,” which it concluded suggests Ionescu is “unconcerned with controlled or delayed release as most of these formulation types do not provide such control.”⁴ Paper 7(DOI), 45.

The generic discussion of liquid formulations in Ionescu and Atadja would not have made it obvious to select a non-enteric coated tablet formulation for 5-

⁴ Patent Owner notes that Petitioner only discusses “liquid syrups” in the Petition. Pet., 37. While Petitioner cites to “coated tablets, capsules, or pulvules” of Ionescu and “tablet, capsule or syrup” of Atadja (Pet., 8), Petitioner does not discuss how capsules and/or pulvules are relevant, and never points to, or relies on, other formulations such as lozenges. Patent Owner reserves the right to file a motion to strike any arguments related to formulations not relied on in the Petition.

azacytidine. Ex.2051(Berkland Decl.), ¶¶105-107. As an initial matter, the liquid formulations in those references are purely hypothetical. Neither Ionescu nor Atadja provides any working examples or data of liquid syrup formulations for oral administration in a therapeutically effective amount or that such formulations overcame the long-understood instability challenges. *See* Sections II.C-II.D; Ex.2051(Berkland Decl.), ¶106.

In any event, the liquid formulation in Ionescu or Atadja would not have motivated a POSA to pursue a therapeutically effective amount of 5-azacytidine in a non-enterically coated **tablet** with a reasonable expectation of success. Liquid formulations and tablets are different, and bioavailability cannot be assumed for different dosage forms, even if both are oral dosage forms. Ex.2051(Berkland Decl.), ¶107. Instead, a POSA understood that many factors influence the efficacy of pharmaceuticals including the chemical and physical properties of the drug and the dosage choice. *See* Ex.2067(Aulton), 2-3, 133; Ex.2051(Berkland Decl.), ¶107. For instance, it was known that “[a] given drug may... show differences in its bioavailability from one type of dosage form to another [even] when given by the same route....” *Id.*, 133. A POSA would not glean from these disclosures of a liquid syrup that a non-enteric coated tablet would be therapeutically effective. Ex.2051(Berkland Decl.), ¶107.

4. When read as a whole, a POSA would not credit Ionescu or Atadja as disclosing or relating to therapeutically effective oral formulations of 5-azacytidine

It is undisputed that neither Ionescu nor Atadja discloses any actual, working examples of oral formulations for 5-azacytidine. *E.g.*, Ex.2050(Buckton Tr.), 72:3-9, 71:6-72:2, 73:19-74:2, 72:10-19, 67:1-9; 66:6-22, 64:16-22. Indeed, neither Ionescu nor Atadja is focused on the dosage form for 5-azacytidine. Ex.2051(Berkland Decl.), ¶108. Ionescu addresses novel crystalline forms of 5-azacytidine. Ex.1004 (Ionescu), 1:8-10, 2:7-9; Ex.2051(Berkland Decl.), ¶108. And Atadja addresses combinations of histone deacetylase inhibitors (HDAs) with any of several known chemotherapeutic agents (including 5-azacytidine). Ex.1005(Atadja), Abstract, 9:15-22:5; Ex.2051(Berkland Decl.), ¶108.

To the extent that Ionescu or Atadja address dosage forms at all, their discussion is limited to generic, boilerplate descriptions of pharmaceutical dosage forms. Ex.1004(Ionescu), 12:12-14:31; Ex.1005(Atadja), 26-27. Neither Ionescu nor Atadja addresses the known instability of 5-azacytidine, let alone purports to solve those problems with any novel dosage forms. Ex.2051(Berkland Decl.), ¶109.

In the context of their disclosures (which as a whole are focused on matters other than dosage forms), a POSA would not have been motivated to look to either Ionescu or Atadja to solve the decades-old problem of formulating an oral dosage

form for 5-azacytidine. Ex.2051(Berkland Decl.), ¶110. Those references provide no insight on that issue beyond the same generic teachings of any formulation treatise. Ex.2051(Berkland Decl.), ¶110. Ionescu discloses dozens of different dosage forms and provide one example of an injection formulation. Ex.1004(Ionescu), 12:12-14:31; Ex.2050 (Buckton Tr.), 71:6-72:2; Ex.2051(Berkland Decl.), ¶110. In fact, the majority of the formulations in Ionescu are incompatible with what was understood about 5-azacytidine at the time because they typically either use high levels of water (*e.g.*, capsules, elixirs, suspensions, solutions, syrups, emulsions, pills), are incompatible with chemotherapeutic drugs (*e.g.*, lozenges), or are routes of administration. Ex.1006(Gibson), -0070, -0073, -0082; Ex.2051(Berkland Decl.), ¶¶111-112 (citing Ex.1030-0038(Remington); Ex.2146(Remington 1990), 296, 1523, 1527, 1530, 1629; Ex.2147(Remington 2005 II), 325-326, 716, 749, 754, 757, 1028; Ex.2065(Ansel), 682; Ex.2144(Lieberman Vol. 1), 438; Ex.2145(Dean), 82-83, 152-153, 397, 538-539). Atadja discloses over a hundred chemotherapeutic agents and generally states that they can be administered via four different formulations. Ex.1005(Atadja), 2-27. This disclosure reflects the knowledge at the time. Some of the agents were known to be administered orally, while others, like 5-azacytidine, were known to be administered via injection. Ex.2051(Berkland Decl.), ¶110; Ex.2053(Blum Decl.), ¶¶24-25, 27, 31 (citing Ex.2075(Craig), 50;

Ex.2133(Exemestane), 1; Ex.2134(Anastrozole), 1; Ex.2135(Letrozole), 1;
Ex.2137(Cytarabine), 8; Ex.2138(Dacogen), 1, 6; Ex.2139(Mitoxantrone), 2, 14).
When considering the disclosures of Ionescu and Atadja as whole, it is clear they
do not motivate or disclose a therapeutically effective oral dosage form of 5-
azacytidine. Ex.2051(Berkland Decl.), ¶113.

Any alleged motivation to select a non-enteric coated tablet formulation is
driven by hindsight. Petitioner's expert, Dr. Buckton, admitted that he did not
consider the teachings of Atadja or Ionescu as a whole. Ex. 2050(Buckton Tr.),
74:20-76:15, 78:13-79:15, 79:22-80:9, 127:9-128:3, 131:14-133:2. For Ionescu,
Dr. Buckton did not consider whether the long list of formulations disclosed were
all compatible with 5-azacytidine. Ex. 2050(Buckton Tr.), 74:20-76:15. For
Atadja, Dr. Buckton admits that he considered all of the formulations to be viable
for 5-azacytidine, and he did not consider any of the other chemotherapeutic agents
in Atadja or how they were administered. Ex. 2050(Buckton Tr.), 127:9-128:3,
128:4-19, 129:16-130:6, 130:7-131:21, 132:13-133:2. A POSA would understand
that Atadja unremarkably discloses a list of chemotherapeutic agents that would be
administered according to their known administration methods, not that every
chemotherapeutic agent would be administered in all of the ways disclosed.
Ex.2053(Blum Decl.), ¶27. Any motivation to select a non-enteric tablet

formulation of 5-azacytidine based on these references is hindsight driven.

Ex.2051(Berkland Decl.), ¶113.

B. Petitioner Has Failed to Establish a Reasonable Expectation of Success

Petitioner's obviousness grounds also fail to establish that a POSA would have had a reasonable expectation of success in arriving at a non-enteric coated tablet of 5-azacytidine that would deliver a "therapeutically effective amount" of the drug to a patient (claim 1), let alone treat MDS or AML (claim 28).

1. Given the well-established instability of 5-azacytidine, a POSA would not have had a reasonable expectation that a non-enteric coated tablet formulation would have been therapeutically effective

Given the state of the art in December 2008, a POSA would not have had a reasonable expectation of success in developing a therapeutically effective, non-enteric coated oral tablet of 5-azacytidine. A POSA would have understood that the compound would likely be degraded before it could be absorbed or maintained in a sufficient amount in the plasma to provide a therapeutic benefit.

Ex.2051(Berkland Decl.), ¶¶114-115; *see* Sections II.C-II.D. Those challenges would have led a POSA to pursue enterically coated tablet formulations of 5-azacytidine to protect the drug from degradation before it could reach the site of absorption. Indeed, that is exactly what the prior art taught before the invention of the '628 patent. Ex.2044(WO2008/028193), ¶[00192] (enteric "formulation is

delivering 5-azacytidine to the colonic region, and that site is capable of efficiently absorbing 5-azacytidine without the degradation associated with cytidine deaminase.”); Ex.2051(Berkland Decl.), ¶115. And the inventors of the '628 patent themselves initially followed that conventional wisdom before serendipitously discovering that 5-azacytidine could be administered orally in a non-enterically coated tablet. *See* Section III.A; Ex.2054(Etter Decl.), ¶¶23-25; Ex.2051(Berkland Decl.), ¶115.

Petitioner's experts acknowledge the problems of chemical degradation of 5-azacytidine were known (Ex.1002(Buckton Decl.), ¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46), but the Petition fails to address this issue in its obviousness analysis. In fact, the Petition provides no expert analysis as to why there would have been a reasonable expectation of success in arriving at the claimed non-enteric coated tablet of 5-azacytidine in view of the known challenges of orally

administering 5-azacytidine. Pet., 38, 61-62; Ex.2051(Berkland Decl.), ¶116.⁵

And the references underlying Petitioner's obviousness grounds do not address that issue either. Indeed, Ionescu and the other references underlying the Petition's obviousness grounds do not disclose any working examples of a non-enterically coated tablet that provides a therapeutically effective amount of 5-azacytidine to patients, nor do they discuss why an oral dosage form of 5-azacytidine did not need to be protected from degradation, contrary to expectations in the field.

Ex.2051(Berkland Decl.), ¶116; *see* Section VI. Petitioner's obviousness challenge fails because it does not address the known challenges to formulating a non-enterically coated tablet of 5-azacytidine to orally administer a therapeutically effective amount of the drug.

⁵ Dr. Buckton noted that 5-azacytidine is an "unusual case" because the drug is "very old" and there is literature that is "probably not credible" so you would need to "obtain your own information to determine what's credible and what's not credible." Ex. 2050(Buckton Tr.), 38:5-11. But neither Dr. Buckton's declaration nor the Petition did that. The Petition does not explain why the references relied upon in the Grounds are credible and would provide a reasonable expectation of success at making the claimed invention, nor what information was not credible and why it would be discounted.

2. Preliminary bioavailability data for unknown oral formulations does not provide a reasonable expectation that a non-enteric coated tablet of 5-azacytidine would be therapeutically effective

Petitioner's assertion that a POSA would have had a reasonable expectation of success in view of "the knowledge in the art that 5-azacytidine was orally bioavailable and well tolerated" (Pet., 38 (cross-citing Section IV.A.3)), fails for multiple reasons.

First, the "knowledge in the art" cited by Petitioner is the Pharmion-PR (Ex. 1010) and Stoltz (Ex. 1034), but neither discloses a *non-enteric coated* tablet formulation. *See* Sections VI.D, VIII.A.2.b. If anything, those references would have led a POSA to believe that an *enteric coated* tablet was required to achieve oral bioavailability, which is consistent with contemporaneous patent filings relating to that work. *See* Section VIII.A.2.b; Ex.2051(Berkland Decl.), ¶¶117-118.

Second, bioavailability alone does not establish obviousness of a therapeutically effective formulation. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (bioequivalence alone could not establish obviousness because "skilled artisans could not predict whether any particular [pharmacokinetic] profile, including a bioequivalent one, would produce a therapeutically effective formulation."). Petitioner puts forth no evidence or reasoning as to why a POSA would reasonably

expect that an 80mg dose with 18% bioavailability relative to Vidaza® would produce therapeutically effective pharmacokinetic properties. Ex.2052(Grass Decl.), ¶81; Ex.2051(Berkland Decl.), ¶119.

Pharmion-PR does not suggest that the 80mg oral dose itself was a therapeutically effective amount of 5-azacytidine, and that was not the purpose of the study reported in Pharmion-PR. Ex.2053(Blum Decl.), ¶¶25, 29-31 (citing Ex.2141(Martinez), 620). On the contrary, Pharmion-PR discloses, and Dr. Buckton agrees, that a POSA would need to conduct a dose escalation study to assess whether the drug could be given at a dose that is both efficacious and non-toxic given the risk-benefit profile for the drug. Ex.1010(Pharmion-PR); Ex.2050(Buckton Tr.), 101:13-20, 106:5-107:1; Ex.2051(Berkland Decl.), ¶119; Ex.2052(Grass Decl.), ¶¶23,86,90; *see also* Ex.1011(Pharmion-PR II).

Because oral drug absorption is a complex process, a POSA would not draw any expectations about the pharmacokinetic profile for an orally administered drug from intravenous or subcutaneous pharmacokinetic data. Ex.2052(Grass Decl.), ¶¶16-24; Ex.2078(Dressman), 11-15; Ex.2122(Toutain), 455, 462-463; Ex.2148(Gibaldi), 322, 337. Given the different pharmacokinetic profiles between subcutaneous, intravenous, and orally administered drugs, coupled with 5-azacytidine's known instability and high metabolism, without performing further studies a POSA would have no reasonable expectation of success that a non-enteric

coated tablet of 5-azacytidine could be given in a therapeutically effective amount (i.e., an amount that was both effective as well as safe and tolerable).⁶

Ex.2052(Grass Decl.), ¶¶23-24. In short, bioavailability in a dog study, followed by Pharmion-PR's disclosure, provides no reasonable expectation that an 80mg or higher doses administered as a non-enteric coated tablet would be therapeutically effective as required by the challenged claims. Ex.2053(Blum Decl.), ¶¶25, 29-31.

Third, the Petition discloses no reliance on Dr. Batchelor's pharmacokinetic modeling to support a reasonable expectation of success. Pet., 38. But to the extent Petitioner subsequently seeks to rely on Dr. Batchelor's declaration for this purpose, that should be foreclosed as both untimely and substantively flawed. *See* Section VIII.E.2; Ex.2052(Grass Decl.), ¶¶44, 75. Dr. Buckton only understood that the predicted pharmacokinetic values are "acceptable" with the benefit of hindsight. Ex.1002(Buckton Decl.), ¶119. Indeed, subcutaneous 5-azacytidine achieves an AUC and C_{max} for 75mg/m² of 960.53±458.06 and 750±403, respectively (*see* Ex.1017-0004(Marcucci); Ex.1007-0009(Vidaza® Label 2004)), which is well above the values predicted by Dr. Batchelor's model. Without the disclosure of the '628 patent, a POSA would have no expectation that the much

⁶ In fact, Petitioner acknowledges that drugs can be ineffective when they degrade quickly in the stomach. Pet., 40.

lower pharmacokinetic values for a non-enteric coated tablet predicted by Dr.

Batchelor would be therapeutically effective. Ex.2052(Grass Decl.), ¶¶80-81; *see also id.*, 93-95, 98.

3. The claims are not obvious to try because a non-enteric coated tablet would not have been a predictable solution for 5-azacytidine

Petitioner cannot demonstrate that Ionescu renders the claims obvious to try. Pet., 37-38. Petitioner provides no analysis as to why such a “sugar-coated” non-enteric coated tablet is one of a finite number of options, as it is not even disclosed in Ionescu. Nor can Petitioner establish that this is predictable and would provide a reasonable expectation of success, particularly in view of the voluminous art establishing that 5-azacytidine, if released in the stomach, would rapidly breakdown. Ex.2051(Berkland Decl.), ¶121. Indeed, Petitioner’s assertions that this invention would have been obvious to try cannot be reconciled with the actual development history of 5-azacytidine (*see* Sections II.C-II.D); it does not take over 40 years of research to discover that which is obvious to try.

Atadja does not cure the deficiencies in Ionescu’s disclosure. Atadja does not focus on oral formulations of 5-azacytidine, and a POSA reading Atadja would have understood that while certain other disclosed chemotherapeutic agents may have been administered orally, 5-azacytidine would be administered as a parenteral injection given that *only* this administration method was known and FDA-

approved. *See* Sections II.C-II.D; Ex.2053(Blum Decl.), ¶¶25, 27. A POSA would not have had a reasonable expectation of success in formulating 5-azacytidine as a non-enteric coated tablet, and nothing in Atadja's disclosure of methods of administering HDAI-chemotherapeutic combinations changes that. Ex.2052(Berkland Decl.), ¶122.

In short, even if a POSA would have been motivated to make an oral tablet of 5-azacytidine (which Petitioner has not shown), Petitioner fails to address that a POSA would have been motivated to formulate an *enteric coated* tablet to protect 5-azacytidine—not a non-enteric coated tablet. Petitioner offers no support for the proposition that a non-enteric coated tablet would predictably deliver a “therapeutically effective amount” of the drug to a patient (claim 1), let alone treat MDS or AML (claim 28). *See* Sections VIII.B.1-VIII.B.2; Ex.2052(Berkland Decl.), ¶¶123-124. Furthermore, “where the prior art, at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1356-1357 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine*, 676 F.3d at 1073). At best, Petitioner's obvious to try argument relies on an unsupported premise that non-enteric coated tablets are the “default” for all drugs (*see* Section VIII.A.2), and this

cannot sustain a conclusion that the claimed invention would have been obvious to try.

C. Ionescu, Atadja, Gibson, and Knowledge of a POSA Do Not Render Obvious Claims 6, 7, or 32

Claims 6 and 7 depend from claim 1 and recite that the composition “is essentially free of cytidine deaminase inhibitor,” or “tetrahydrouridine.”

Ex.1001('628 patent), claims 6-7. Claim 32 depends from claim 28 and recites the method does not comprise “co-administering a cytidine deaminase inhibitor...”

Id., claim 32.

First, because Ionescu, Atadja, Gibson and Vidaza® do not disclose examples of oral administration of 5-azacytidine, they do not address the issue of whether to use a cytidine deaminase inhibitor with it. Ex.2052(Berkland Decl.), ¶126.

Second, Petitioner argues that a POSA would know that cytidine deaminase inhibitors were ineffective. But Petitioner relies on an incomplete understanding of how and why they are used. Dr. Buckton only considered one inhibitor, THU, and was generally unfamiliar with these inhibitors by 2008. Ex.2050(Buckton Tr.), 95:10-96:5, 96:6-9; Ex.2051(Berkland Decl.), ¶127. Petitioner's reliance on Kelley (Ex.1015) is misplaced because it relates to cytosine arabinoside (ara-C) with THU and not 5-azacytidine, and it does not address any cytidine deaminase inhibitors other than THU. Ex.1015(Kelley), Abstract; Ex.2051(Berkland Decl.),

¶127. Dover (Ex.1031), also cited by Petitioner, discloses that patients with sickle cell disease only responded to 5-azacytidine when cytidine deaminase inhibitor THU and 5-azacytidine were used together. Ex.1031(Dover), 528. Thus, Dover shows that cytidine deaminase inhibitors, including THU, were considered for administration with 5-azacytidine for treating sickle cell disease, which was consistent with the state of the art that 5-azacytidine is degraded by cytidine deaminase. Ex.2051(Berkland Decl.), ¶127. As of December 2008, the use of enzyme inhibitors was a strategy to improve oral bioavailability due to the significant degradation by cytidine deaminase. *Id.*, Ex.2041(WO2008/028193), ¶[0007]. Petitioner has not identified any motivation other than Kelley and Dover to refrain from co-administering a 5-azacytidine inhibitor, including THU, with 5-azacytidine, but both of those references fail to establish motivation for the reasons discussed above. Moreover, a POSA would have had no reasonable expectation of success in orally administering 5-azacytidine without a cytidine deaminase inhibitor, especially a non-enteric coated tablet formulation of 5-azacytidine. Ex.2051(Berkland Decl.), ¶¶127-128; Ex.2017(Gaubert), 837-838. At least for these additional reasons, Petitioner has not established claims 6, 7, or 32 would have been obvious over Ionescu in view of Atadja, Gibson, and the knowledge of a POSA.

D. Ionescu, Atadja, Gibson, and Knowledge of a POSA Do Not Render Obvious the Doses Recited in Claims 9, 24-27, and 36

Claim 24 depends from claim 1 and recites that “the amount of 5-azacytidine is at least about 300 mg.” Ex.1001('628 patent), claim 24. Claims 9, 25-27, and 36 recite doses of at least about 360mg, 400mg, or 480mg. The independent claims, and thus also these dependent claims, require that the non-enteric coated tablet “compris[e] a therapeutically effective amount of 5-azacytidine.” None of the art cited by Petitioner teaches a therapeutically effective amount of 5-azacytidine for a non-enteric coated tablet or that the therapeutically effective amount is at least about 300mg (or 360mg, 400mg, 480mg). Ex.2051(Berkland Decl.), ¶129. Instead, Petitioner argues it would have been obvious to optimize the dosage amounts of the non-enteric coated tablets of Ionescu based on Atadja. Pet., 44-45.

Consistent with its disclosure of only a subcutaneous formulation, Ionescu discloses a 200mg maximum 5-azacytidine dose, which is close to the approved maximum dose for Vidaza®. Ex.1007-0022(Vidaza® Label 2004) (dose of 100mg/m² (~190mg/day) for the average adult); Ex.2051(Berkland Decl.), ¶130. Nowhere does Ionescu disclose an oral formulation comprising 300mg of 5-azacytidine, and Atadja specifically skips certain dosages, including 300mg. Ex. 1004(Ionescu), 14:22-25; Ex.1005(Atadja), 27:13-16. Atadja does not provide any support that its broad range would be therapeutically effective for 5-azacytidine

administered as a non-enteric coated tablet, and it provides no reason to select the claimed dosage amounts from the range of 200-1000mg, especially when 300mg is not recited. Further, a POSA would not have understood Atadja to be directed to non-enteric coated oral tablets of 5-azacytidine, and therefore a POSA would not have looked to the reference as describing doses that are therapeutically effective in a tablet. Ex.2051(Berkland Decl.), ¶131.

Petitioner argues that a POSA would have increased the dose from 200mg towards bioequivalence with subcutaneous Vidaza® and relies on Pharmion-PR to argue that there was reasonable expectation of success because the safety and oral bioavailability had already been established. Pet., 46-48. As explained above, Pharmion-PR does not disclose that a non-enteric coated tablet formulation is safe and effective and only reports on administering 80mg orally using an undefined formulation (which a POSA would understand to be enteric coated). *See* Section VIII.A.2.b; Ex.2053(Blum Decl.), ¶¶25, 29. Petitioner points to no evidence supporting any reasonable expectation that a 300mg dose, or any higher doses of 5-azacytidine would achieve pharmacokinetic properties that were therapeutically effective and safe given the known challenges with hydrolysis and degradation. Ex.2051(Berkland Decl.), ¶¶132-133.

E. Ionescu, Atadja, Gibson, and Knowledge of a POSA Do Not Render Obvious The Pharmacokinetic Values Required by Claims 11, 12, 18-22 and 38-43

Claims 11, 12, 18-22, and 38-43 recite specific pharmacokinetic values produced by the claimed compositions and methods of treatment. Petitioner cites no express disclosure of these pharmacokinetic values in the prior art and instead argues that they are inherently disclosed. Pet., 48-50. As discussed below, however, the Petition does not discuss any particular formulation. Ex.2052(Grass Decl.), ¶47. Dr. Batchelor's *in silico* modeling is not predictive because it is based on default values and assumptions and does not account for well-known stability concerns. Ex.2052(Grass Decl.), ¶¶49-75, 80-81. Finally, Dr. Buckton's calculations are fatally flawed and unreliable. Ex.2052(Grass Decl.), ¶¶82-88.

1. Petitioner's inherency argument fails at least because the prior art does not disclose a non-enteric coated tablet

A finding of obviousness based on inherency is improper where "[a] person of ordinary skill in the art thus would not have had a reason to select the claimed formulation from the prior art ranges or to modify [a disclosed formulation] to arrive at the claimed formulation." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015). Inherency is a "high standard," that is "carefully circumscribed in the context of obviousness." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Unlike in *Persion v. Alvogen*, where the prior art administered exactly the same formulation as the patent-in-suit, here

Petitioner relies on a tablet coated with sugar in Ionescu, which is not identical to the formulation in the '628 patent that achieves the claimed pharmacokinetic values. *See* Pet., 49. Indeed, Ionescu fails to disclose the composition of its “sugar-coated” tablet. Ex.1004(Ionescu), 13:11-21; Ex.2051(Berkland Decl.), ¶¶111.

As explained above, the claimed pharmacokinetic values result from the administration of the formulations disclosed in the specification. *See* Section VII.C. Pharmacokinetic values are dose- and formulation-dependent. *See, e.g.*, Ex.1001('628 patent), Fig. 12 (depicting different pharmacokinetic area-under-the-curve values for 5-azacytidine administered as non-enteric (“F3”) and enteric (“F4”) formulations and administered as different doses for the same formulation); Ex.2052(Grass Decl.), ¶¶47-48. None of the references discloses a formulation for a non-enteric coated tablet of 5-azacytidine with the non-enteric film-coated composition disclosed in the '628 patent; thus, Petitioner has not shown that the prior art formulation necessarily or inherently results in the claimed pharmacokinetic values. Ex.2052(Grass Decl.), ¶¶77-79.

2. Dr. Batchelor's modeling is faulty and does not indicate the claimed pharmacokinetic values are inherent to any formulation

Petitioner's reliance on Dr. Batchelor's modeling is misplaced because the modeling is fatally flawed and unreliable. *See* Pet., 29-31, 50-51.

First, although 5-azacytidine's degradation in acidic solutions was well-documented (*see* Sections II.C-II.D; *see* Ex.2054(Etter Decl.), ¶9), Dr. Batchelor modeled the degradation using hydrolysis rates for pH4.5, despite the pH of the stomach being pH1.1. *See* Ex.1003(Batchelor Decl.), ¶¶34-36, 41; Ex.2049(Batchelor Tr.), 124:2-4, 135:17-136:5. Thus, Dr. Batchelor's model does not properly account for the level of hydrolysis a POSA would have expected for a non-enteric coated tablet. Ex.2052(Grass Decl.), ¶¶64-67, 75.

Second, despite known cytidine deaminase metabolism of 5-azacytidine resulting in no biological activity (Ex.2017(Gaubert)), Dr. Batchelor entirely fails to account for this metabolism, which is not included in the default parameters of the modeling software that she used. Ex.2049(Batchelor Tr.), 114:1-6, 114:20-115:3; Ex.2052(Grass Decl.), ¶¶53-59, 75 (citing Ex.2148(Gibaldi), 294). Dr. Batchelor also confirmed she did not model any first-pass metabolism, despite Marcucci reporting that 5-azacytidine is subject to significant levels of metabolism. Ex.2049(Batchelor Tr.), 103:17-104:4, 109:10-109:16; Ex.2052(Grass Decl.), ¶¶53-54, 60-63, 75.

Third, Dr. Batchelor admits that she relied upon the default values for several modeling parameters, such that several of her input values are untethered to real-world data. Ex.1003(Batchelor Decl.), ¶¶43-46; Ex.2049(Batchelor Tr.), 65:2-12, 91:21-92:1, 92:5-19, 117:17-119:3, 119:4-120:1, 76:15-77:9, 79:15-80:3;

Ex.2052(Grass Decl.), ¶¶68-71. Dr. Batchelor confirmed that measured values are preferred and did not undertake any parameter testing to evaluate whether her assumptions or reliance on these default values was reasonable.

Ex.2049(Batchelor Tr.), 141:21-142:17; Ex.2052(Grass Decl.), ¶¶68-71;
Ex.2107(Porta), 226-227.

Fourth, Dr. Batchelor did not model any specific formulation attributes, including a tablet with a sugar-coating or a particular excipient.

Ex.2049(Batchelor Tr.), 126:5-12; Ex.2050(Buckton Tr.), 108:19-109:11;
Ex.2052(Grass Decl.), ¶¶50-52.

Fifth, Dr. Batchelor did not validate her modeling as is standard in the field. Ex.1039 at 1779-1780; Ex.1044, 96; Ex.2049(Batchelor Tr.), 142:22-143:18, 143:21-144:14, 143:15-144:6, 160:6-13, 159:15-160:5, 164:22-165:18; Ex.2052(Grass Decl.), ¶¶ 72-74; Ex.2048(Pawar), 5. Indeed, Dr. Batchelor's results for the 400mg dose are simply double those for the 200mg dose, which is hardly surprising as she used default linear relationships in her GastroPlus model, which are not validated against any real-world data for 5-azacytidine. Ex.2052(Grass Decl.), ¶¶72-74.

These flaws in Dr. Batchelor's analysis render her conclusions unreliable and untethered to what would be achieved in the real world. Ex.2052(Grass Decl.), ¶¶42, 45. The Board therefore should disregard Dr. Batchelor's unreliable

testimony, as well as any portions of Dr. Buckton's testimony or the Petition relying upon Dr. Batchelor's testimony. Ex.2052(Grass Decl.), ¶¶80-81, 89, 98.

3. Extrapolation using Vidaza® pharmacokinetics and Pharmion-PR's bioavailability does not render obvious claims 11 and 38

For claims 11 and 38, Petitioner presents an additional inherency argument that relies on reported pharmacokinetic data from Pharmion-PR (Ex.1010) and subcutaneously administered 5-azacytidine (Ex.1017(Marcucci)) to predict the AUC claim limitations. Pet., 52-53 (citing Ex.1002(Buckton Decl.), ¶167)). Petitioner's use of relative bioavailability from Pharmion-PR is impermissible for Ground 2 because Pharmion-PR is not part of the Ground. Irrespectively, Pharmion-PR is entirely silent on its formulation, and a POSA would have understood it to be enterically coated. *See* Section VIII.A.2.b. Furthermore, the calculations presented do not correctly apply basic principles of pharmacokinetics to arrive at these hindsight driven results. Ex.2052(Grass Decl.), ¶¶43, 82-88. First, Petitioner does not account for the differences in dose between the subcutaneous data, which uses a dose of 142.5mg for the average adult, and the 80mg oral dose of Pharmion-PR. As Dr. Grass explains, when the AUC for subcutaneous dose is scaled to account for the differences in dose, 18% of Vidaza®'s subcutaneous AUC is 97 ng-h/mL, which does not meet the claim limitation of at least about 200 ng-hr/mL. Ex.2052(Grass Decl.), ¶¶82-85.

Second, the '628 patent's disclosure belies Petitioner's faulty assumption that percentage bioavailability would remain constant with an increased dose so that a blanket value of 18% could be applied to the AUC values achieved with different dosages. *See, e.g.*, Ex.1001('628 patent), Fig. 14, Fig. 19; Ex.2052(Grass Decl.), ¶¶86-88. Petitioner provides no evidence that a POSA would expect 18% relative oral bioavailability with higher doses. Thus, the AUC values achieved for subcutaneous administration of Vidaza® would not render obvious the claimed AUC parameters in claims 11 and 38. Ex.2052(Grass Decl.), ¶¶88-89, 98.

IX. THE '628 PATENT CLAIMS ARE NOT OBVIOUS IN VIEW OF IONESCU IN VIEW OF PHARMION-PR, ATADJA AND GIBSON AND THE KNOWLEDGE OF A POSA (GROUND 3)

In Ground 3, Petitioner relies on Pharmion-PR solely to provide a motivation to select dosage form and amounts from Ionescu and does not cite it as disclosing a claim limitation. *Id.*, 59-61. However, as discussed above, Pharmion-PR's disclosure that an unspecified oral formulation of 80mg was 18% bioavailable compared to Vidaza® provides no such motivation or reasonable expectation of success. *See* Sections VIII.A.2.b, VIII.B.2. The lack of reasonable expectation of success is supported by Pharmion-PR II, which notes that the maximum tolerated dose, dose limiting toxicities, safety, pharmacokinetics and pharmacodynamic effects of oral 5-azacytidine were all yet to be determined. Ex.1011(Pharmion-PR II); Ex.2052(Grass Decl.), ¶90; Ex.2051(Berkland Decl.),

¶134. Thus, for the same reasons addressed under Ground 2, Petitioner has failed to establish that Ionescu, Pharmion-PR, Atadja, and Gibson and the knowledge of a POSA render obvious the challenged claims under Ground 3. Ex.2051(Berkland Decl.), ¶134.

X. OBJECTIVE INDICIA REINFORCE THE NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS

“[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record” concerning nonobviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Here, this objective evidence reinforces the non-obviousness of the challenged claims.

A. Long-felt But Unmet Need

Each year, about 20,000 patients are diagnosed with AML, which is an aggressive form of blood cancer that often leads to death. Ex.2071(Carter), 1; Ex.2042(European Medicines Report), 8; Ex.2064(Altman), 16-17; Ex.2073(Cogle), 1405; Ex.2053(Blum Decl.), ¶12. Standard AML therapy was aimed at achieving remission followed by short-term therapy to eradicate residual leukemia, and there were no oral treatments available. Ex.2071(Carter), 2-3; Ex. 2111(Reville), 1; Ex.2072(Choi), 1416; Ex.2053(Blum Decl.), ¶¶13, 36, 47. However, relapse was more likely than not. Ex. 2111(Reville), 1; Ex.2053(Blum Decl.), ¶13.

Moreover, there was a particular need for maintenance therapies for patients with AML. As recognized in the literature, “[m]ost patients with AML currently will relapse” (Ex.2073(Cogle), 1409), and the “outcomes for patients with early recurrence of AML are dismal” (Ex.2125(Vigil), 224). *See also* Ex.2080(Ellison), 509; Ex.2110(Récher); Ex.2082(Frisch), 683; Ex.2053(Blum Decl.), ¶34.

Improved patient outcomes required prolonged remissions achieved by maintenance therapies. Ex.2073(Cogle), 1409; Ex.2118(Sorrentino), 20; Ex.2053(Blum Decl.), ¶34. For nearly 50 years, researchers searched for AML maintenance therapies without success. *See, e.g.*, Ex.2080(Ellison); Ex.2108(Preisler), 1442-1443; Ex.2097(Löwenberg); Ex.2093(Lammers), 1196; Ex.2125(Vigil), 224; Ex.2119(Southall), 1; Ex.2072(Choi), 1416; Ex.2053(Blum Decl.), ¶¶33, 35-36.

The need for a maintenance therapy for AML persisted even after the development of injectable 5-azacytidine (Vidaza®), which is approved only for use in patients with MDS, not patients with AML. Ex.1007-0005(Vidaza® Label 2004); Ex.1008-0005(Vidaza® Label 2007). Moreover, there were significant drawbacks to the use of injectable 5-azacytidine, where administration is uncomfortable and inconvenient. Ex.2125(Vigil), 227; Ex.2118(Sorrentino), 20; Ex.2004(Beisler), 281; Ex.2053(Blum Decl.), ¶32. Thus, there remained a long-felt need to discover orally administered formulations of 5-azacytidine even after

the development of an injectable formulation of the drug. Ex.2053(Blum Decl.), ¶¶14-15, 31; Ex.2087(Grønbæk), 395; Ex.2029(Stresemann), 8; Ex.1014(Chan), 807; Ex.2003(Aparicio), 631.

Indeed, in recognition of the long-standing need for an effective maintenance therapy for AML, the FDA granted Fast Track designation to Pharmion's development of oral azacytidine. Ex.1011-0005(Pharmion-PR II); Ex.2053(Blum Decl.), ¶¶15, 39-40.

The invention of the '628 patent satisfied the long-felt need for a maintenance therapy for AML, as well as the long-felt need for an orally administered formulation of 5-azacytidine. Ex.2095(Liu), 13; Ex.2130(Weill Cornell), 1; Ex.2053(Blum Decl.), ¶¶32-38, 40. The invention of the '628 patent is embodied by the drug Onureg®. Ex.2051(Berkland Decl.), ¶¶147-149. Onureg® is the first FDA-approved drug specifically as maintenance treatment for AML patients and is “the first drug... to improve survival as maintenance therapy for acute myeloid leukemia patients,” nearly doubling the average overall survival and average relapse-free survival compared to placebo. Ex.2091(Kipp) Abstract, 2569; Ex.2053(Blum Decl.), ¶44.

B. Skepticism and Failure of Others

As discussed above, researchers had been interested in developing a therapeutically effective formulation of 5-azacytidine since the compound was first

discovered in the 1960s. *See* Sections II.C-II.D. Many researchers studied the drug, but none had successfully developed a therapeutically effective orally administered formulation of 5-azacytidine despite over 40 years of research.

Ex.2051(Berkland Decl.), ¶¶137-138; *see* Sections II.C-II.D.

Due to those decades of failed research efforts, there was significant skepticism as to whether a non-enteric oral formulation of 5-azacytidine could be developed at all. Given the drug's well-known instability (*see* Sections II.C-II.D) that skepticism persisted even after the approval of Vidaza® in 2004.

Ex.2051(Berkland Decl.), ¶138; Ex.2018(Kaminskas); Ex.2070(Ben-Kasus); Ex.2022(Mund); Ex.2029(Stresemann); Ex.2010(Chen); Ex.2132(Ziemba).

Indeed, to the extent that the field considered oral azacytidine, that research focused on *enteric* coated formulations that would protect the drug from the acidic environment of the stomach. *See* Ex.1001('628 patent), 3:58-63; *see also* Ex.2041(WO2008/028193); Ex.1021(Sands), ¶¶[0029]-[0030]; Ex.2051(Berkland Decl.), ¶139.

The invention of the '628 patent overcame the decades of skepticism and failure of others to demonstrate for the first time that it was possible to develop a therapeutically effective oral formulation of 5-azacytidine with a non-enteric coated tablet. Ex.2051(Berkland Decl.), ¶¶136-140. Moreover, this was contrary

to the prevailing understanding that an orally administered formulation would require an enteric coating. Ex.2054(Etter Decl.), ¶¶30-31; Section III.A.

C. Unexpected Results

Because of the well-established belief that 5-azacytidine was chemically and enzymatically unstable and poorly permeable (Ex.2041(WO2008/028193), ¶[0007]), there was a prejudice in the art against developing a non-enteric coated oral tablet formulation of 5-azacytidine. Ex.2054(Etter Decl.), ¶¶9, 19-21; Ex.2051(Berkland Decl.), ¶141. Indeed, as explained above, to the extent oral formulations were considered, the focus was on protecting 5-azacytidine from the acidic environment of the stomach by, *e.g.*, enteric coatings (Ex.2051(Berkland Decl.), ¶141; *see also* Ex.1001('628 patent), 3:58-65) or took another approach completely (*see, e.g.*, Ex.2132(Ziemba); Ex.1021(Sands)). In part because of this prejudice backed-up by over forty years of research and publications, it was unexpected that non-enteric tablets of 5-azacytidine exhibited impressive pharmacokinetic, pharmacodynamic, and clinical properties. Ex.2054(Etter Decl.), ¶¶33-35; Ex.2051(Berkland Decl.), ¶141.

Compared to enterically coated tablets, non-enteric coated tablets of 5-azacytidine resulted in higher peak plasma concentrations of 5-azacytidine, shorter delays to the peak concentration, greater recipient exposure to 5-azacytidine, and higher bioavailability for recipients. *See* '628 at Figures 8-10, 12, 13, 14; 8:63-9:5;

71:56-72:17 (Table 11); 72:39-67; Ex.2054(Etter Decl.), ¶34; Ex.2051(Berkland Decl.), ¶142. Despite being exposed to the harsh gastric environment, non-enteric coated tablets of 5-azacytidine surprisingly provided faster, higher, and greater exposure to the compound than tablets protected from this environment by an enteric coating.⁷

Indeed, even in preliminary tests, the 5-azacytidine exposure achieved through administration of the non-enteric coated tablets of the invention was “comparable or better than the exposure observed” following administration of a formulation described as having a “leaky” enteric coating. Ex.1051-0018(61/201,145). As credited by the Patent Office, “[T]hese results are significant and surprising, particularly given the conventional wisdom at the time... that 5-azacytidine would decompose in the acidic environment...” Ex.1022-2091, -2138-2139.

⁷ To the extent that Petitioner asserts that Ionescu is the closest prior art to which the invention's pharmacokinetic values must be compared, nowhere does Ionescu (or Atadja, Gibson, or Pharmion-PR) provide any pharmacokinetic values. Further, Petitioner's reliance on Dr. Batchelor's modeling is unavailing because it is faulty. *See* Section VIII.E.2.

Additionally, the lower drug exposure provided by non-enterically coated 5-azacytidine tablets provided surprisingly effective clinical results compared to higher levels achieved by intravenous administration. For example, researchers comparing subcutaneously injected to orally administered 5-azacytidine found that, although the oral administration only achieved a comparable bioavailability of 20%, the “[k]inetics of the change in DNA methylation levels after [subcutaneous] and oral azacitidine were similar...” Ex.2084(Garcia-Manero), 440; Ex.2051(Berkland Decl.), ¶143. Thus, oral 5-azacytidine’s ability to achieve similar methylation results associated with positive clinical outcomes despite a lower bioavailability than subcutaneous doses, demonstrates a surprising and unexpectedly significant result. *See, e.g.*, Ex.2054(Etter Decl.), ¶35; Ex.2051(Berkland Decl.), ¶143.

As such, a POSA would not have expected to arrive at the pharmacokinetic values recited in claims 11, 18, 38, and 40. Indeed, researchers have recognized oral 5-azacytidine as “a different drug” than parenterally administered 5-azacytidine because of their “distinct PK profiles....” Ex.2086(Griffiths), 440. Thus, even starting with injectable 5-azacytidine, researchers and clinicians could not have expected to arrive at the therapeutic efficacy of the independent claims (Ex.2051(Berkland Decl.), ¶¶141-144) or the pharmacokinetic values recited in the dependent claims (Ex.2052(Grass Decl.), ¶93-95, 97-98).

D. Industry Praise

Even before FDA approval, clinicians recognized Onureg® as a major development in the field of oncology. Ex.2104(Perl), 2287; Ex.2068(Bankhead), 2; Ex.2053(Blum Decl.), ¶41. This “transformative” advance was praised as “represent[ing] a potential new standard of care for patients” that would “change practice once [non-enteric oral 5-azacytidine] is available.” Ex.2103(Oral CC-486); Ex.2053(Blum Decl.), ¶41; *see also* Ex.2114(Slater), 2; Ex.2129(Wei), E86. Indeed, non-enteric, oral 5-azacytidine was the “first time [clinicians] ha[d] seen an oral drug that can lead to improved relapse-free survival and overall survival” in older AML patients, leading other clinicians to hail it as “practice-changing.” Ex.2103(Oral CC-486); Ex.2053(Blum Decl.), ¶¶41, 46.

After approval, Onureg® was hailed as part of a “period of breakthrough drug approvals for AML.” Ex.2094(Lin 2022), 1; Ex.2089(Kantarjian), 581; Ex.2053(Blum Decl.), ¶41. Onureg® “became the first FDA approved drug specifically as maintenance treatment for AML patients” (Ex.2095(Liu), 13) and was called “[t]he biggest advance in AML maintenance currently,” stating that the “paradigm [of post-complete remission care] may[]be set to change” thanks to Onureg®. Ex.2111(Reville), 1,7; *see also* Ex.2081(FDA Approves Oral Azacitidine); Ex.2053(Blum Decl.), ¶¶37, 42, 46.

Additionally, as Dr. Blum explains, Onureg®'s success "highlights the potential for routes of administration that facilitate new protocols for low, continuous dosing of chemotherapeutics, such as 5-azacytidine, that permits 'a more sustained cellular exposure.'" Ex.2053(Blum Decl.), ¶¶43, 46; Ex.2102(Odenike), 461; Ex.2084(Garcia-Manero), 2526; Ex.2073(Cogle), 1404. Researchers also credited the "extended dosing schedules enabled by oral administration" in overcoming 5-azacytidine's instability and limited bioavailability "by increasing exposure to cycling malignant cells" and thereby "potential[ly]... enhance[ing] clinical activity of azacitidine...." Ex.2073(Cogle), 1406; Ex.2053(Blum Decl.), ¶¶43, 46. This previously unavailable extended treatment regimen allowed for before unavailable maintenance therapy opportunities for patients. Ex.2053(Blum Decl.), ¶43. Because such "[m]aintenance treatment is given for a prolonged period," "it needs to be easy to give and well tolerated." Ex.2091(Kipp), Abstract; *see also* Ex.2086(Griffiths), Abstract; Ex.2053(Blum Decl.), ¶44. POSAs have praised the non-enteric coated tablets' role in removing burdensome physical and logistical challenges preventing patients from more readily obtaining their treatment. Ex.2053(Blum Decl.), ¶¶44, 46. Clinicians have also praised it for reducing side effects associated with injected therapeutics. *See, e.g.*, Ex.2091(Kipp), Abstract; Ex.2086(Griffiths),

Abstract; Ex.2115(Sochacka-Ćwikła), 15; Ex.2120(Steensma), 388;
Ex.2125(Vigil), 227; Ex.2118(Sorrentino), 20; Ex.2053(Blum Decl.), ¶45.

E. Nexus

Nexus is presumed “when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them.” *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022) (internal quotations omitted). This does not require a perfect correspondence between products and claims, but a demonstration that “the product is essentially the claimed invention.” *Id.*, 1418 (citation omitted).

Here the '628 patent is listed in the Orange Book for Onureg®. Onureg® embodies claims 1, 2, 6-8, 11, 13-18, 20-24, 28, 32-35, 38, 40, 42, and 43. *See* Ex.2051(Berkland Decl.), ¶¶147-149. These include claims specifically reciting dosages and pharmacokinetic values. The secondary considerations relied on are attributed to the commercial product Onureg® and all critical features of Onureg® are covered by these claims of the '628 patent, thus the claimed invention is coextensive with Onureg® and there is a presumed nexus. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374-1375 (Fed. Cir. 2019).

XI. CONCLUSION

For the above reasons, Patent Owner respectfully requests that the Board uphold the challenged claims.

Respectfully submitted,

Date: October 12, 2023

By: /Heather M. Petruzzi/
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CERTIFICATION UNDER 37 C.F.R. §42.24(d)

I hereby certify that the foregoing, Patent Owner's Response, contains 13,993 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d), excluding the parts of the exempted from the word count by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

I hereby certify that on October 12, 2023, I caused a true and correct copies of the following materials:

- Patent Owner's Response
- Patent Owner's Exhibit List
- Exhibits 2048-2060, 2062-2068, 2070-2098, 2100-2104, 2107-2108, 2110-2112, 2114-2116, and 2118-2151
- Word Count Certification Under 37 C.F.R. § 42.24(d) to be served via e-mail on the following attorneys of record:

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