

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

CELLGENE CORPORATION,
Patent Owner.

IPR2023-00512
Patent 8,846,628 B2

Before TINA E. HULSE, RYAN H. FLAX, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION
Granting Instituting *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Celgene Corporation (“Patent Owner”) is the owner of U.S. patent 8,846,628 B2 (“the ’628 patent”). Paper 5, 1. On February 10, 2023, Apotex Inc. (“Petitioner”) filed a Petition for *inter partes* review challenging the patentability of claims 1, 2, 6–9, 11–28, 32–36, and 38–43 of the ’628 patent (claims 3–5, 10, 29–31, and 37 are not challenged). Paper 1, 1, 6 (“Pet.”). On May 15, 2023, Patent Owner filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). No further briefing was requested or authorized.

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute trial in an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any preliminary response filed under § 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

After reviewing the parties’ submissions, we conclude Petitioner demonstrates a reasonable likelihood it will prevail in showing that at least one challenged claim of the ’628 patent is unpatentable under the presented grounds. Therefore, we grant institution of *inter partes* review. Our reasoning is discussed below.

A. REAL PARTIES-IN-INTEREST

Petitioner lists Apotex Inc., Apotex Corp, Apotex Pharmaceutical Holdings Inc, and Aposherm Delaware Holdings Corp., as well as SK Capital Partners, LP, as real parties-in-interest. Pet. 4. Patent Owner identifies itself and Bristol-Myers Squibb Company as real parties-in-interest. Paper 5, 1.

B. RELATED MATTERS

Petitioner identifies *Celgene Corp. v. Accord Healthcare Inc.*, 1-21-cv-01795 (D. Del.) as a related matter. Pet. 4. Patent Owner identifies the same matter as related. Paper 5, 1.

C. THE '628 PATENT

The '628 patent issued on September 30, 2014, from U.S. Application 12/466,213, which was filed on May 14, 2009. Ex. 1001, codes (45), (21), (22). The '628 patent ultimately indicates priority to U.S. Provisional Applications 61/053,609, filed on May 15, 2008, 61/201,145, filed on December 5, 2008, and 61/157,857, filed on March 5, 2009. *Id.* at code (60), 1:5–12. Petitioner asserts that, for priority, the '628 patent is entitled to no earlier than the December 5, 2008, filing date of provisional 61/201,145. *See, e.g.*, Pet. 19. At this point, Patent Owner does not dispute this and applies the December 5, 2008, date to the challenged claims.¹ Prelim. Resp. 5 n.1.

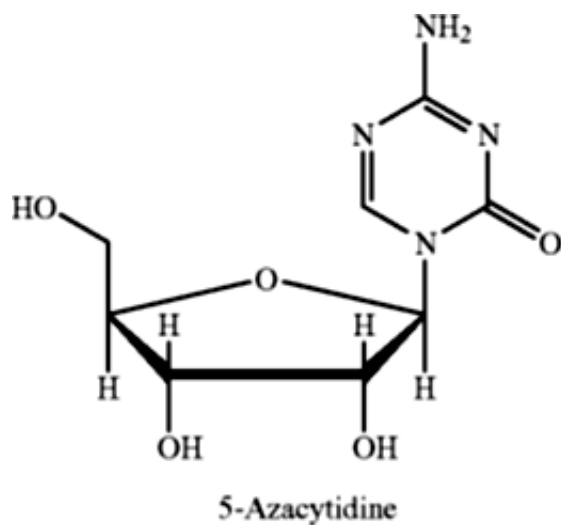
The '628 patent's abstract states:

The present disclosure provides pharmaceutical compositions comprising cytidine analogs, for example, 5-azacytidine or decitabine, for oral administration, wherein the compositions release the cytidine analog, for example, 5-azacytidine or decitabine, substantially in the stomach. Also provided are methods of treating diseases and disorders using the oral formulations provided herein.

Id. at Abstract.

¹ Regardless of which, if any, provisional application affords an earlier effective filing date for the '628 patent for priority purposes, on this record, it appears that each asserted reference has an earlier publication date, making each reference prior art and any potential disagreement over the '628 patent's priority immaterial to our decision. *See infra* Section II.D.

As Background, the '628 patent identifies that “[c]ancer is a major worldwide public health problem” and specifically discusses myelodysplastic syndromes (MDS), which may progress and convert into leukemia, one form being acute myelogenous leukemia (AML). *Id.* at 1:28–67. The Background section of the '628 patent further describes that “[n]ucleoside analogs have been used clinically for the treatment of viral infections and cancer. Most nucleoside analogs are classified as anti-metabolites. After they enter the cell, nucleoside analogs are successively phosphorylated to nucleoside 5'-mono-phosphates, di-phosphates, and tri-phosphates.” *Id.* at 2:27–32. The Background describes “5-Azacytidine, also known as azacytidine, AZA, or 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one, is currently marketed as the drug product VIDAZAR®” and that “5-Azacytidine is a nucleoside analog, more specifically a cytidine analog.” *Id.* at 2:33–39. The molecular structure of 5-azacytidine is shown to be:



Id. at 2:44–62. The image above shows 5-Azacytidine (or just Azacytidine) as being a two-ring molecule (one 5-membered ring and one 6-membered

ring) of molecular formula $C_8H_{12}N_4O_5$ and, of particular note, having a nitrogen rather than carbon at position 5 of a cytosine ring. *Id.* at 2:39–46.

Citing to prior publications, the Background of the '628 patent describes that “5-Azacytidine [has] been tested in clinical trials and showed significant anti-tumor activity, such as, for example, in the treatment of myelodysplastic syndromes (MDS), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and non-Hodgkin’s lymphoma (NHL),” and that the drug is “approved for subcutaneous (SC) or intravenous (IV) administration to treat various proliferative disorders,” but that “[o]ral dosing of cytidine analogs would be more desirable and convenient.” *Id.* at 3:28–51.

As to such oral dosing, the '628 patent states that

oral delivery of cytidine analogs has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor permeability. For example, cytidine analogs have been considered acid labile and unstable in the acidic gastric environment. Previous attempts to develop oral dosage forms of cytidine analogs have required enteric coating of the drug core to protect the active pharmaceutical ingredient (API) from what was understood and accepted to be therapeutically unacceptable hydrolysis in the stomach, such that the drug is preferably absorbed in specific regions of the lower gastrointestinal tract, such as the jejunum in the small intestine.

Id. at 3:54–65.

Upon turning to describing its invention, the '628 patent states that “[p]rovided herein are pharmaceutical compositions comprising cytidine analogs, wherein the compositions release the API substantially in the stomach upon oral administration.” *Id.* at 4:21–23. The '628 patent describes embodiments having non-enteric-coated tablets comprising the cytidine analog. *Id.* at 4:44–48. The '628 patent describes such

formulations as including 5-azacytidine doses of about 40–1,000 mg, to achieve, upon oral administration and substantial release in the stomach, an area-under-the-curve (AUC) value of at least about 200–400 ng-hr/mL, a maximum plasma concentration ($C_{\max}$) of at least 100 ng/mL, and a time to maximum plasma concentration ($T_{\max}$) of less than about 90 minutes. *Id.* at 5:48–6:10, 33:35–38:6.

The '628 patent describes that known and conventional methods can be used to make the 5-azacytidine formulations and describes a variety of embodiments, including those with coatings that can be applied to a tablet or capsule comprising 5-azacytidine, so that it is released substantially in the stomach, for example a sugar layer coating. *Id.* at 37:20–40:44. The '628 patent also describes that the 5-azacytidine dose in the oral formulations can be adjusted based on the patient's characteristics, e.g., age, weight, prior treatment regimens, and other variables, as known in the art, or to increase the drug's beneficial effect, but not cause toxicity. *Id.* at 76:66–77:20.

The '628 patent includes Section VI.A titled "DEFINITIONS," and expressly provides several definitions for terms used in the Specification and claims. The '628 patent defines that:

The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, or 0.05% of a given value or range.

Id. at 9:57–65. The '628 patent also defines that:

the terms “therapeutically effective amount” and “effective amount” of a compound mean an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. A “therapeutically effective amount” and “effective amount” of a compound mean an amount of therapeutic agent, alone or in combination with one or more other agent(s), which provides a therapeutic benefit in the treatment or management of the disease or disorder. The terms “therapeutically effective amount” and “effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

Id. at 10:43–57. The ’628 patent further defines that:

The term “non-enteric-coated,” when used herein, refers to a pharmaceutical composition, formulation, or dosage form that does not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine). In certain embodiments, a non-enteric-coated composition, formulation, or dosage form is designed to release the active ingredient(s) substantially in the stomach.

Id. at 11:42–48. The ’628 patent also defines that:

The term “substantially in the stomach,” when used herein in reference to a composition, formulation, or dosage form provided herein, means that at least about 99%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 70%, at least about 65%, at least about 60%, at least about 55%, at least about 50%, at least about 45%, at least about 40%, at least about 35%, at least about 30%, at least about 25%, at least about 20%, at least about 15%, or at least about 10% of the cytidine analog is released in the stomach. The term “released in the stomach” and related terms as used herein refer to the process whereby the cytidine analog is made available for uptake by or transport across cells lining the stomach and then made available to the body.

Id. at 11:49–62. The '628 patent also defines that:

The term “subject” is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In specific embodiments, the subject is a human.

Id. at 11:63–67.

Nowhere in the '628 patent's written description does it expressly describe specifically how its invention overcame the professed difficulty in developing a therapeutically effective oral formulation of azacytidine related to the indicated chemical instability (acid lability and instability in the acidic gastric environment), enzymatic instability, and/or poor permeability, noting only that formulations could be prepared by conventional methods known to those skilled in the field. *See generally id.*

The '628 patent concludes with 43 claims, of which claims 1 and 28 are independent claims. Ex. 1001, 81:55–84:23. Claim 1 is illustrative and reproduced below:

1. [1a] A pharmaceutical composition for oral administration comprising [1b] a therapeutically effective amount of 5-azacytidine and [1c] at least one pharmaceutically acceptable excipient, [1d] wherein the composition is a non-enteric coated tablet.

Ex. 1001, 81:55–58 (adding sub-numbers as used by Petitioner).

Independent claim 28 is similar to claim 1 in reciting the same drug, formulated as a non-enteric coated (NEC)² tablet, but is directed to a method of using that drug composition to treat myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). *Id.* at 82:61–83:2. The dependent

² NEC refers to non-enteric coatings/coated and EC refers to enteric coatings/coated.

claims further define the composition of the 5-azacytidine NEC tablet, the dose of 5-azacytidine, or the resultant pharmacokinetic (PK) measurements (area under the curve value (AUC), maximum plasma concentration ($C_{\max}$), and time to maximum plasma concentration ($T_{\max}$) upon oral administration (pharmacokinetics addresses how the body interacts with administered substances). *See id.* at 81:59–61, 82:5–60, 83:12–84:23.

D. ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts the following grounds for the unpatentability of claims 1, 2, 6–9, 11–28, 32–36, and 38–43 of the '628 patent:

Ground	Claims Challenged	35 U.S.C. § ³	Reference(s)/Basis
1	1, 2, 6–8, 11, 13–18, 20–23, 28, 32–35, 38, 40, 42, 43	102(b)	Ionescu ⁴
2	1, 2, 6–9, 11–28, 32–36, 38–43	103(a)	Ionescu, Atadja, ⁵ Gibson ⁶
3	1, 2, 6–9, 11–28, 32–36, 38–43	103(a)	Ionescu, Atadja, Gibson, Pharmion-PR ⁷

³ The '628 patent has a priority date no later than its actual filing date of May 14, 2009, which is before the AIA revisions to 35 U.S.C. §§ 102 and 103 took effect on March 16, 2013. 35 U.S.C. § 100 (note). Therefore, pre-AIA §§ 102 and 103 apply. However, our decision is not impacted by which version of the statute applies.

⁴ WO 2004/082619 A2, published Sept. 30, 2004 (Ex. 1004, “Ionescu”).

⁵ WO 2004/103358 A2, published Dec. 2, 2004 (Ex. 1005, “Atadja”).

⁶ TAYLOR & FRANCIS GROUP, PHARMACEUTICAL PREFORMULATION AND FORMULATION, A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM (Mark Gibson ed. 2001) (Ex. 1006, “Gibson”).

⁷ Pharmion, *News Release, Clinical Data Presented on Pilot Pharmacokinetic Study of Oral Azacitidine, Bioavailability data from First Oral Demethylating Agent in Clinical Trials*, (July 9, 2007) (“Presented at the American Society of Clinical Oncology 43rd Annual Meeting”) (Ex. 1010, “Pharmion-PR”). Petitioner and affiant assert Pharmion-PR was

See Pet. 6.

In support of these grounds for unpatentability, Petitioner submits, *inter alia*, the Declarations of Graham Buckton, PhD (Ex. 1002) and Hanna K. Batchelor, PhD (Ex. 1003). In response, Patent Owner submits, *inter alia*, the Declaration of Cory Berkland, PhD. Ex. 2001. In the absence of evidence to the contrary, we find Drs. Buckton, Batchelor, and Berkland competent to testify on the subject matter of their declarations. *See infra* Section II.A; *see* Ex. 1002 ¶¶ 3, 5–13, 15–19, Exhibit A; Ex. 1003 ¶¶ 3, 5–13, 15–17, Exhibit A; Ex. 2001 ¶¶ 2–15, 17, 28–30, App’x A.

II. DISCUSSION

A. LEVEL OF ORDINARY SKILL IN THE ART

In determining the level of ordinary skill in the art, we consider the types of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

We do not discern that Petitioner expressly advocates for any specific definition of the ordinarily skilled artisan, which is a reading of the Petition that Patent Owner confirms. *See generally* Pet.; Prelim. Resp. 17. However, as identified by Patent Owner (*see* Prelim. Resp. 17), each of Petitioner’s witnesses, Drs. Buckton and Batchelor, states,

published at <https://web.archive.org/web/2007079161226/http://investor.pharmion.com/phoenix.zhtml?c=142045&p=irol-newsArticle&ID=1010376&highlight=>. *See* Ex. 1010 (Affidavit of Nathaniel E Frank-White regarding “the Wayback Machine”).

A POSA relating to the subject matter of the '628 patent would have had (1) a Pharm.D., or a Ph.D. in pharmaceutical sciences, chemical engineering, chemistry, or related discipline; and (2) at least two to four years of experience with pharmaceutical design, formulation, development, and/or manufacturing of oral dosage forms. A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team to solve a given problem. To the extent necessary, this person would have worked in collaboration with others with the requisite education and experience in candidate drug selection, clinical use, clinical testing, design, formulation, development, and/or manufacturing of pharmaceutical oral dosage forms.

Ex. 1002 ¶ 17; Ex. 1003 ¶ 16.⁸ As does Patent Owner, we understand this to be Petitioner's proposed definition of the person of ordinary skill in the art and to what it refers when addressing a POSA throughout the Petition.

Patent Owner neither contests this proposed definition of the ordinarily skilled artisan nor offers its own. Prelim. Resp. 17–18.

For the purposes of this Decision, we accept the above quoted definition of the person of ordinary skill in the art (or ordinarily skilled artisan), which appears to be consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '628 patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“the prior art itself [may] reflect[]” evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

⁸ The parties and their witnesses use “POSA” to refer to the person of ordinary skill in the art.

B. CLAIM CONSTRUCTION

The Board interprets claim terms in an *inter partes* review using the same claim construction standard that is used to construe claims in a civil action in federal district court. 37 C.F.R. § 42.100(b). In construing claims, district courts and the Board here, by default, give claim terms their ordinary and customary meaning, which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Should claim terms require express construction, sources for claim interpretation include “the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.” *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). “[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms.” *Id.* However, the claims “do not stand alone,” but are part of “‘a fully integrated written instrument’ . . . consisting principally of a specification that concludes with the claims,” and, therefore, the claims are “read in view of the specification.” *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995) (en banc)). Any special definition for a claim term must be set forth in the specification “with reasonable clarity, deliberateness, and precision.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Without such a special definition, however, limitations may not be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Our claim construction positions herein are necessarily preliminary, by the nature of the proceeding. Further argument by the parties is permitted.

Regarding claim construction, Petitioner states, “[t]he ’628 patent defines several claim terms including, for example, ‘about,’ ‘therapeutically effective amount,’ ‘non-enteric-coated,’ and ‘subject.’ (EX-1001 at 9:57-65, 10:43-48, 11:42-38, 11:63-67[.]) Petitioner applies the definitions set forth in the ’628 patent (*id.* at 9:51-13:9) unless otherwise noted [in the Petition].” Pet. 20; *see supra* Section I.C (identifying that the ’628 patent expressly defines certain relevant terms).

We note that the terms “therapeutically effective amount” and “non-enteric-coated tablet” (we add “tablet” to this claim phrase for full context) appear in claims 1 and 28. Ex. 1001, 81:55–58, 82:61–83:2. Further, “about” appears in claims 5, 8–12, 18–22, 24–27, 31, and 35–43. *Id.* at 82:1–84:23. The term “subject” appears in claims 11, 12, 18–22, 28, and 38–43. *Id.* at 82:15–84:23.

Patent Owner, similar to Petitioner, urges we apply the ’628 patent’s Specification’s expressly-provided definition of “non-enteric-coated” (“non-enteric-coated tablet,” contextually, as noted above). Prelim. Resp. 18.

The Federal Circuit in *Phillips* states, “our cases recognize that the specification may reveal a special definition given to a claim term by the

patentee that differs from the meaning it would otherwise possess. In such cases, the inventor’s lexicography governs.” *Phillips*, 415 F.3d at 1316 (citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). Moreover, “[w]hen the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.” *Multiform Dessicants, Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998). We agree with the parties that the ’628 patent expressly defines this term in stating “[t]he term ‘non-enteric-coated,’ when used herein, refers to *a pharmaceutical composition, formulation, or dosage form that does not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine)*,” and we adopt this express definition herein with regard to “non-enteric coated tablet.”⁹ Ex. 1001, 11:42–48 (emphasis added).

Regarding the scope of this claim term, we note that this definition of “non-enteric coated,” urged by each party and expressly set forth in the Specification, only requires what the pharmaceutical composition, formulation, or dosage, i.e., the “tablet” recited by claims 1 and 28, does not include—“*does not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine)*” (emphasis added); that is, the limitation does not require any coating be *applied* to the *tablet*. Nothing in claims 1 or 28 expressly requires any coating whatsoever. A requirement for a coating is introduced at dependent claim 13, which recites

⁹ We note that, when used in the claims, this term does not include a hyphen between the words enteric and coated where, in the written description of the ’628 patent, such a hyphen is included; however, we discern no substantive difference between the two phrases and none is asserted by the parties.

“the tablet [of claim 1] further comprises a sugar coating, a film coating, or a compression coating.” Ex. 1001, 82:21–23, cert. of correction.

Our understanding and interpretation of this aspect of the claims is supported by the Specification, which states, *inter alia*, “[i]n particular embodiments, the tablet contains a drug core that comprises a cytidine analog, and [only] *optionally further contains a coating* of the drug core,” and “embodiments provide the aforementioned compositions, which: are immediate release compositions; *do not have an enteric coating* (i.e., *are non-enteric-coated*); are tablets,” and “[i]n certain embodiments, *coatings and/or shells may be employed* in the formulation to control the release of the cytidine analog . . . substantially in the stomach,” and, further, describes a variety of tablet designs for controlling drug delivery to occur in the stomach. *Id.* at 4:65–5:1, 5:52–55, 34:48–50, 38:41–41:62 (emphasis added). This description makes clear that some embodiments have a coating and some do not.

Our understanding of this claim language is also reinforced by Patent Owner’s (then Applicant) statements to the Office during prosecution of the ’628 patent. *See* Ex. 1022. Applicant argued in its last Response (dated February 27, 2017) to an office action before the allowance and issuance of the claims that “[a] novel and unique element of the claimed composition is the absence of an enteric coating, *i.e.*, a coating that is designed to release the active ingredient beyond the acidic environment of the stomach when orally administered.” *Id.* at 2072–73. This crystallizes the Patent Owner’s understanding of the claim term “non-enteric coated tablet” before the Office, i.e., it is a tablet without an enteric coating.

Thus, per the claim language itself, the Specification as a whole, and the prosecution history, “non-enteric coated tablet” refers to the recited “tablet” itself as omitting an enteric coating and does require any specific coating be included in the tablet.

Patent Owner also argues that the term “test subject” (which is similar to, and sometimes associated with, but not identical to the claim term “subject”), which appears in claims 11, 12, 18–22, and 38–43, means “a human or other animal who received the recited pharmaceutical composition in connection with a test of the recited parameter.” Prelim. Resp. 18–19 (also asserting Petitioner does not appear to dispute this construction).

We first note that the term “test subject” appears in the ’628 patent only in the claims. *See generally* Ex. 1001. However, we find Patent Owner’s definition comports with the Specification’s express definition of “subject,” a term the Specification appears to use synonymously with the claim term “test subject” and the word *patient*, and that Patent Owner’s definition adds that the *subject* received the pharmaceutical composition in connection with a *test* of the recited parameter, which we find to be a reasonable interpretation of the claim term “test subject,” in accordance with the plain language of the claims on their face, and as supported by the relevant portions of the Written Description that describe testing parameters relating to drug administration. Ex. 1001, 35:45–36:62, 67:61–81:48. We adopt Patent Owner’s definition herein.

Patent Owner also argues that the language of claim 14, and claim 15 that depends from 14, does further limit the scope of the subject matter of claim 13 from which claim 14 depends. Prelim. Resp. 19. Patent Owner

provides no support for this position. *Id.* We need not resolve this matter at this stage of the proceeding.

We determine that no other express construction of any claim term is necessary for purposes of rendering this Decision. *See Nidec Motor Corp.*, 868 F.3d at 1017.

If either party intends to further argue claim construction at trial they should do so in a clearly designated section of their briefing so as to expressly identify such arguments. *See, e.g.*, 37 C.F.R. § 42.104(b)(3) (content of petition); *see also* Board’s Consolidated Trial Practice Guide (CTPG), 84 FR 64280, 46, 48–45 (Nov. 2019) (available at <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf?MURL=>). Critical claim construction arguments should not be relegated to or hidden within patentability arguments on the facts.

C. LEGAL STANDARDS FOR ANALYZING PATENTABILITY

“In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner.¹⁰ *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

¹⁰ Although we refer herein to certain of Patent Owner’s arguments as being not persuasive, we do not shift the ultimate burden of proof from Petitioner. Such non-persuasiveness is in the context of the parties’ arguments and the record as a whole.

An *inter partes* review may be instituted if the information presented by Petitioner in the Petition, in view of Patent Owner's Preliminary Response and the preliminary record, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. 35 U.S.C. § 314.

“Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference.” *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). To anticipate “it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). “However, a reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

A prior art reference without express reference to a claim limitation may anticipate by inherency. See *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). “Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.” *Id.* (quoting *MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)).

Regarding obviousness, the Supreme Court in *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for

determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;¹¹ and (4) considering objective evidence indicating obviousness or non-obviousness.¹² *KSR*, 550 U.S. at 406.

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the answer depends on “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417.

With these standards in mind, and in view of the definition of the ordinarily skilled artisan and claim interpretation above, we address Petitioner’s challenges below.

D. PETITIONER’S ASSERTED PRIOR ART

1. *Ionescu (Ex. 1004)*

Ionescu is a WIPO international patent application publication dated September 30, 2004. Ex. 1004, 1 (codes (10), (43)). There is currently no dispute that *Ionescu* is prior art. *See generally* Prelim. Resp. In fact, *Ionescu* is listed on the face of the ’628 patent in its References Cited section

¹¹ *See supra* Section II.A.

¹² At this point, there is no asserted evidence pertaining to objective indicia of non-obviousness. *See* Prelim. Resp.

as a foreign patent document, evidencing it is prior art. Ex. 1001, page 2 (code (56)).

Ionescu's Abstract states: "The invention provides novel polymorphic and pseudopolymorphic crystalline forms of 5-azacytidine, along with methods for preparing said forms, wherein 5-azacythidine [*sic*] is represented by the formula (I). The invention also includes pharmaceutical compositions comprising said forms." Ex. 1004, Abstract (code (57)). Similarly, at its Field of the Invention section, Ionescu discloses: "The invention relates to the isolation of crystalline polymorphic and pseudopolymorphic forms of 5-azacytidine (also known as azacitidine and 4-amino-1- β -D-ribofuranosyl-S-triazin-2(1*H*)-one). 5-azacytidine may be used in the treatment of disease, including the treatment of myelodysplastic syndromes (MDS)." *Id.* at 1.

Ionescu discloses pharmaceutical formulations including 5-azacytidine, which the reference calls the "drug product," in unit dose form, along with a pharmaceutically acceptable carrier, diluent, or excipient. *Id.* at 12. Ionescu discloses that such formulations can be capsules, tablets, pills, lozenges, or other containers, as well as provided in elixirs, suspensions, emulsions, solutions, and syrups, and also injectable solutions. *Id.* As excipients, Ionescu lists, *inter alia*, microcrystalline cellulose, mannitol, sorbitol, sucrose, glucose, and magnesium stearate. *Id.* at 12–13. Ionescu states 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." *Id.* at 13.

Ionescu discloses that, “[i]n certain embodiments of the invention, the 5-azacytidine forms(s) [*sic*] may be made into the form of dosage units for oral administration.” *Id.* Ionescu discloses its tablets can be “coated tablets,” if “desired” and if so, they “may be coated with a concentrated solution of sugar.” *Id.* Ionescu discloses that such sugar coatings “may contain gum arable, gelatin, talc, titanium dioxide, or with a lacquer dissolved in the volatile organic solvent or mixture of solvents,” and that dyes may be added. *Id.*

Ionescu discloses that its

Tablets for oral use are typically prepared in the following manner, although other techniques may be employed. The solid substances are gently ground or sieved to a desired particle size, and a binding agent is homogenized and suspended in a suitable solvent. The 5-azacytidine form(s) and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension. The moistening typically causes the particles to aggregate slightly, and the resulting mass is gently pressed through a stainless steel sieve having a desired size. The layers of the mixture are then dried in controlled drying units for a pre-determined length of time to achieve a desired particle size and consistency. The granules of the dried mixture are gently sieved to remove any powder. To this mixture, disintegrating, anti-friction, and anti-adhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size.

Id. at 13–14.¹³.

Ionescu also discloses 5-azacytidine “[l]iquid preparations for oral administration,” prepared as “solutions, syrups, or suspensions.” *Id.* at 14.

¹³ We note that application of a sugar coating is not indicated as a part of this “typical” preparation.

Ionescu discloses that “the pharmaceutical formulations of [its] invention are preferably prepared in a unit dosage form, each dosage unit containing from about 5 mg to about 200 mg, more usually about 100 mg of the 5-azacytidine form(s)” and that “‘unit dosage form’ refers to physically discrete units suitable as unitary dosages for human subjects/patients or other mammals, each unit containing a predetermined quantity of the 5-azacytidine polymorph calculated to produce the desired therapeutic effect, in association with preferably, at least one pharmaceutically acceptable carrier, diluent, or excipient.” *Id.* at 14.

Ionescu makes no mention of including or requiring “a cytidine deaminase inhibitor” or “tetrahydrouridine” in any pharmaceutical formulation including 5-azacytidine. *See generally id.*

2. *Atadja (Ex. 1005)*

Atadja is a WIPO international patent application publication dated December 2, 2004. Ex. 1005, 1 (codes (10), (43)). There is currently no dispute that Atadja is prior art. *See generally* Prelim. Resp.

At its Abstract, Atadja states:

The invention relates to a combination which comprises (a) one or more chemotherapeutic agents and (b) a histone deacetylase inhibitor (“HDAI”) for simultaneous, concurrent, separate or sequential use, especially for use in the treatment of proliferative diseases including pre-malignant lesions (e.g. colon polyps) and malignancies, both solid and undifferentiated or other proliferative diseases in a mammal, particularly a human. The invention also relates to pharmaceutical compositions comprising such a combination and to a method of preventing or treating proliferative diseases including pre-malignant lesions (e.g. colon polyps) and malignancies, both solid and undifferentiated or other proliferative diseases, in a mammal, particularly a human, with such a combination. The

present invention further also relates to a commercial package or product comprising such a combination.

Ex. 1005, Abstract (code (57)). One proliferative disease disclosed to be treated is “leukemias.” *Id.* at 2.

Atadja discloses several “chemotherapeutic agent[s]” that may be the pharmaceutical composition of its invention, one of which is 5-Azacytidine. *Id.* at 26–27; *see also id.* at 33, 34 (discussing or claiming using 5-Azacytidine). Atadja also discloses doses for this pharmaceutical composition, stating “5-Azacytidine is administered at a[n] appropriate dose in the range from 100 to 1500 mg daily, for example, 200-1000 mg/day, such as 200, 400, 500, 600, 800, 900 or 1000 mg/day, administered in one or two doses daily.” *Id.* at 27. Atadja then 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.” *Id.*

3. *Gibson (Ex. 1006)*

Gibson, in relevant part, is a chapter (Ch. 11, authored by Peter Davies and titled “Oral Solid Dosage Forms”) of a book having a copyright date of 2001, which indicates having been cataloged in the Library of Congress. Ex. 1006, 3, 8–87.¹⁴ Gibson is cited in the body of the ’628 patent’s written description as being a “pertinent textbook” disclosing “conventional methods known to those skilled in the field of pharmaceutical formulation” for preparing “the formulations provided.” Ex. 1001, 37:20–

¹⁴ We refer to the pagination added to the footer of this exhibit. Added pages 8–87 correspond to original pages 379–458 of the reference. *See* Ex. 1006.

32. There is currently no dispute that Gibson is prior art. *See generally* Prelim. Resp.

In its introductory paragraph, Gibson states:

In the last 15 to 20 years, there has been a huge resource in both academia and industry devoted to the development of drug delivery systems that target drugs more effectively to their therapeutic site. Much of this work has been successful and is reported within this text. In spite of this, oral solid dosage forms such as tablets and hard gelatin capsules, which have been in existence since the nineteenth century, remain the most frequently used dosage forms.

Ex. 1006, 8. Gibson explains that oral administration “is perhaps the least invasive” and “is a route that the patient understands and accepts,” and “are able to administer . . . themselves.” *Id.* From a manufacturer’s perspective, Gibson discloses that oral doses have “many advantages,” including being cheap technology, stable, compact, and with a versatile appearance. *Id.* Gibson states that “[t]ablets and capsules are also very versatile” and “will continue to remain one of the most used methods of delivering drugs to the patient in the future.” *Id.*

Gibson identifies that solid dosage forms can be formulated to provide a variety of release profiles, such as immediate release, where the drug is released immediately after ingestion, and delayed release, where the drug is not released until a physical event has occurred (time elapsed, pH change, gut flora). *Id.* at 9 (Table 11.2). Gibson identifies several tablet components (excipients) to be used with the active ingredient, such as magnesium stearate as a lubricant, microcrystalline cellulose as a diluent or disintegrant or compression filler or extrudate, mannitol as a compression filler, hydroxypropyl cellulose as a film coating polymer, hydroxypropyl methylcellulose as a granulating agent or film coating polymer,

methycellulose as a granulating agent or film coating polymer. *Id.* at 40 (Table 11.8), 41–42 (Table 11.9), 49 (Table 11.11), 52 (Table 11.12), 57 (Table 11.13), 59–60, 67 (Table 11.15).

Gibson discloses the use of tablet coatings for environmental protection, taste, minimizing contact with drug, appearance, swallowing, mechanical protection, and release properties. *Id.* at 62. Gibson identifies “three main methods used to coat pharmaceutical tablets: sugar coating, film coating and compression coating,” with “[s]ugar coating [being] the most commonly used method until the 1970s, when it was largely superseded by film coating.” *Id.*

Gibson discloses that, “[s]ugar coating, as its name suggests, involves coating tablets with sucrose. This is a highly skilled, multistep process that is very labour intensive. The process involves applying a number of aqueous solutions of sucrose, together with additional components, which gradually build up into a smooth, aesthetically pleasing coat.” *Id.* Gibson discloses that sugar coatings consist of a sealing coat, a subcoat, and a smoothing coat. *Id.* Gibson goes on to describe sugar coating as follows:

One of the reasons for coating tablets is to protect the drug substance from environmental factors such as moisture, so it is important that the coating solution does not penetrate into the core. This is achieved by applying a sealing coat. Traditionally, a coating of shellac dissolved in ethanol was applied, but this has largely been replaced by the use of synthetic water-resistant polymers such as cellululose acetate phthalate or polyvinylacetate phthalate. The challenge for the formulator is to optimise the quantity of subcoat applied to ensure the core is protected while minimising the effect on drug release.

Id. at 63. Gibson discloses the next layer, the subcoat, as a sugar-containing (sucrose) mixture applied to round off the tablet and serve as a smooth

adhesive layer for the following layer. *Id.* Gibson discloses the next layer to be a smoothing coat that also contains sugar (sucrose syrup). *Id.* at 64.

These may be followed by a coloring layer and then a polishing layer. *Id.*

Gibson next discloses that an alternative to a sugar coating is a film coating, which comprises a polymer. *Id.* at 63–68. Gibson discloses ways for forming a film coating and then concludes thereafter that “[i]t has been emphasised to this point that the coat should not delay the release of the drug substance from the tablet,” but that “[i]t is possible to design a coat that will modify the release of a drug substance for a beneficial effect.” *Id.* at 68.

Gibson states that “[t]he 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.” *Id.* at 68. Gibson then states that “[t]he most common method of achieving an enteric coating is to apply a polymer that contains acidic substitutions, thus giving it a pH-dependent solubility profile.” *Id.* at 68; *see also id.* at 70 (Table 11.17—commonly used enteric coating polymers). On this, Gibson concludes that a “[f]ilm coating can also be used to delay the release of drugs. This is normally applied to multiparticulate systems where particles will be coated with differing thicknesses of water-insoluble polymers such as ethylcellulose.” *Id.* at 70.

Regarding the types of tablet coatings and their advantages and disadvantages, Gibson provides the following Table 11.18, reproduced below:

Table 11.18 Coating methods.		
Coating Method	Advantages	Disadvantages
Sugar coating	Elegant final product. Tablets can be printed for identification purposes. Cheap, readily available starting materials. Simple equipment requirements. Excellent protection from environment.	Long process time. Traditional manufacture more an art than a science; high operator dependency. Significantly increases tablet size.
Film coating	Quick process, easy to automate. Negligible increase in tablet size. Tablets can be identified either by printing or through incisions. Minimal effect on drug release. Enteric coating feasible.	Finish not as elegant as sugar coating. Coating process stresses tablet formulation, cores must be robust to resist abrasion and edge chipping during coating.
Compression coating	It is a dry process, so suitable for moisture-sensitive compounds. Can be used for combination products where the active substances are incompatible.	Significant increase in tablet weight. Possible to produce tablets with no inner core.

Id. at 72. The above table describes three coating methods (sugar, film, and compression) and their advantages and disadvantages, noting that film coatings have the advantage of feasibly being enteric, which is not mentioned in relation to sugar coatings. *Id.*

4. *Pharmion-PR (Ex. 1010)*

Pharmion-PR is dated “06/02/2007,” and is a news release relating to a June 2, 2007, report of data from a pilot study on the bioavailability of Pharmion Corporation’s oral dosage formulation of Azacitidine, presented at the 43rd Annual Meeting of the American Society of Clinical Oncology in

Chicago.¹⁵ Ex. 1010, 5–6.¹⁶ Petitioner’s witness, Nathaniel E. Frank-White, a “Records Request Processor at the Internet Archive,” also called the Wayback Machine, testifies that Pharmion-PR, based on its assigned URL, is identified as published no later than July 9, 2007. *Id.* at 1, 4 (Exhibit A). There is currently no dispute that Pharmion-PR is prior art. *See generally* Prelim. Resp.

The most relevant portion of Pharmion-PR states:

Clinical Data Presented on Pilot Pharmacokinetic Study of Oral Azacitidine

Bioavailability Data from First Oral Demethylating Agent in Clinical Trials

Presented at the American Society of Clinical Oncology 43rd Annual Meeting

CHICAGO, June 2 /PRNewswire-FirstCall/ -- Pharmion Corporation (Nasdaq: PHRM) today reported data from a pilot study that demonstrated the bioavailability of the Company's oral dosage formulation of Azacitidine. These data were presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago. (June 1-5, 2007). Pharmion’s epigenetic anti-cancer products, which include Vidaza(R) (azacitidine for injection), MCGD0103 and oral Azacitidine, are being investigated in the treatment of

¹⁵ Pharmion Corporation is identified as the Applicant of Ionescu (Ex. 1004, code (71)). Charles L. Beach, PhD, stated in his declaration submitted during the prosecution of the '628 patent that Celgene Corporation acquired Pharmion Corporation during his employment therewith. Ex. 1022, 2085 (we cite to the added pagination for the prosecution history). Patent Owner states that Pharmion Corporation is “the predecessor company to Patent Owner where the inventors began their work on oral azacytidine formulations.” Prelim. Resp. 24.

¹⁶ Our citations are to the added pagination of the lower right corner at each page of the exhibit.

hematologic malignancies and solid tumors and are the subject of poster and oral presentations at the Meeting.

An oral dosage formulation of Azacitidine would provide a more desirable and convenient route of administration for patients and clinical staff and eliminate injection-site reactions. In addition, it would enable the evaluation of a low-dose regimen that could maximize demethylation and gene re-expression, as well as the evaluation of long-term or maintenance therapy.

The study was designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered Azacitidine in patients with Myelodysplastic Syndromes (MDS), acute myeloid leukemia (AML) or other solid tumors. A total of four patients were enrolled and received study drug. One patient received a 60 mg dose and three patients received a single 80 mg dose. In each case, Azacitidine was well-tolerated and quantifiable in plasma. Following an 80mg dose the bioavailability of the oral formulation of Azacitidine was 18 percent relative to subcutaneous (SC) administered Vidaza. Having established that acceptable plasma concentrations of azacitidine can be achieved with single oral dosing, this pilot study has concluded. A multi-dose escalating study of oral azacitidine is now underway.

“Oral azacitidine represents an extremely exciting opportunity,” said Dr. Guillermo Garcia-Manero, Associate Professor of Medicine and Chief, Section of Myelodysplastic Syndromes, Department of Leukemia, M.D. Anderson Cancer Center. “The potential for a chronic oral demethylating agent will not only apply to MDS but to many other tumor types as well. This is a very important step forward for epigenetic therapies.”

Data Presented Saturday, June 2

Phase I/II study of a novel oral isotype-selective histone deacetylase (HDAC) inhibitor MGCD0103 in combination with azacitidine in patients (pts) with high-risk Myelodysplastic Syndrome (MDS) or Acute Myelogenous Leukemia (AML) - G. Garcia-Manero, MD, MD Anderson Cancer Center; Abstract

#7062; June 2, 2007; 8:00-12:00 pm; McCormick Convention Center, S Hall A2

The combination of 5-azacytidine and valproic acid is safe and active in advanced solid tumors - A.O. Soriano, MD Anderson Cancer Center; Abstract #3547; June 2, 2007; 2:00-6:00pm; McCormick Place Convention Center, S102a

Id. Pharmion-PR also discloses that “Vidaza was the first drug approved for the treatment of all five subtypes of myelodysplastic syndromes (MDS).”

Id.

E. PETITIONER’S PATENTABILITY CHALLENGES

As summarized above, Petitioner asserts three grounds for unpatentability of the claims of the ’628 patent. *See supra* Section I.D; *see also* Pet. 6. We review Petitioner’s challenges and Patent Owner’s arguments below.

As a prelude to presenting its grounds for unpatentability, Petitioner asserts some “background” information on the invention’s claimed subject matter. Pet. 6–18. Petitioner asserts that the claimed drug, 5-azacytidine, was long-known for treating cell proliferation diseases like MDS, having been first developed in the 1960s. *Id.* at 6–7 (citing Ex. 1001, 1:39–67, 2:14–26; Ex. 1023; Ex. 1024; Ex. 1025). Petitioner asserts that a formulation of 5-azacytidine was approved by the FDA for subcutaneous (SC) and intravenous (IV) administration under the trade name Vidaza. *Id.* at 7–8 (citing Ex. 1001, 3:48–50; Ex. 1007; Ex. 1008).

In addition to these approved SC and IV administration techniques, Petitioner also asserts that, prior to the invention, oral administration of 5-azacytidine, including via conventional tablets, was known. *Id.* at 8–13 (citing Ex. 1004; Ex. 1005; Ex. 1010; Ex. 1011; Ex. 1012; Ex. 1016). Petitioner asserts there were also known reasons for those of ordinary skill in

the art to prefer an oral dosage over the SC and IV formulations, for example, known solubility of the drug under physiological conditions, patient convenience and compliance, eliminating complications associated with injections, and maximized demethylation and gene re-expression to improve biological effect. *Id.* at 9–10 (citing Ex. 1001, 37:20–32; Ex. 1002 ¶ 43; Ex. 1004; Ex. 1005; Ex. 1006; Ex. 1010; Ex. 1011; Ex. 1012; Ex. 1019; Ex. 1021; Ex. 1026; Ex. 1029; Ex. 1030; Ex. 1042).

Petitioner asserts that when using conventional methods to make pharmaceutical tablets, whether having a sugar or film coating, non-enteric coatings (NEC) were well known and routinely used, and would have been “the default choice over, and more common than, enteric coatings.” *Id.* at 10–12 (citing Ex. 1001, 37:20–32; Ex. 1004; Ex. 1005; Ex. 1006; Ex. 1019; Ex. 1021; Ex. 1026; Ex. 1029; Ex. 1030). Petitioner asserts that, “absent a compelling reason to select an enteric coating, a POSA would prefer a NEC.” *Id.* at 12.

As discussed below, Patent Owner argues that Petitioner overlooked such a compelling reason.

As its own introduction in response to Petitioner’s, Patent Owner agrees that 5-azacytidine was a well-known cancer drug for decades before the ’628 patent, but counters that it was also well-known to be an unstable compound in an acidic environment like the stomach (and also enzymatically metabolized) and, therefore, no oral formulation had ever been successful and any development directed thereto would have focused on enterically coated tablets.¹⁷ Prelim. Resp. 1, 5–10 (citing, *inter alia*,

¹⁷ Patent Owner states, “[i]n contrast to an enteric coated tablet, a non-enteric coated tablet *does not contain a coating designed to prevent release*

Ex. 1001, 3:58–65; Ex. 1002 ¶¶ 119, 138; Ex. 1003 ¶¶ 34–35, 41; Ex. 1006; Ex. 1014; Ex. 1021; Ex. 1030; Ex. 1034; Ex. 2001 ¶¶ 64–85; Ex. 2014; Ex. 2015; Ex. 2041; Ex. 2043).

Patent Owner asserts that:

The '628 patent explains that “[p]revious attempts to develop oral dosage forms of cytidine analogs have ***required enteric coating of the drug core*** to protect the active pharmaceutical ingredient (API) from what was understood and accepted to be ***therapeutically unacceptable hydrolysis in the stomach***, such that the drug is preferably absorbed in specific regions of the lower gastrointestinal tract....” *Id.* 3:58-65.¹⁸

Id. at 12 (emphasis Patent Owner’s).

Patent Owner argues that the inventors made a “surprising discovery” that it was possible to treat cancer with 5-azacytidine tablets sans enteric coating. *Id.* at 1. Patent Owner argues that Petitioner does not explain how the ordinarily skilled artisan would have addressed the known instability/degradation issue.¹⁹ *Id.* at 5, 12–13.

of the drug in the acidic environment of the stomach. Ex. 1001 ('628 patent), 11:42-45; Ex. 2001 (Berkland Decl.) at ¶49.” Prelim. Resp. 10 (emphasis added). This comports with the parties’ urged interpretation of “non-enteric coated” as discussed above at Section II.B.

¹⁸ As noted above, however, Ionescu, which originated from the same company and/or its predecessor as the '628 patent, does not require an enteric-coated tablet for oral delivery of 5-azacytidine. Thus, Patent Owner’s statement suggests that either the two inventor teams were unaware of each other’s work on methods for oral delivery of the same drug or the drafters of the '628 patent did not consider Ionescu, which was listed on an IDS form, to disclose an attempt to develop an oral dosage form of 5-azacytidine. Given this apparent inconsistency, Patent Owner is encouraged to address this issue at trial.

¹⁹ As we noted above, however, in our review, neither does the '628 patent.

Patent Owner also addresses tablet sugar coatings. Patent Owner argues that merely identifying a coating as a sugar coating is not synonymous with identifying a non-enteric coating because it was possible to make such coatings enteric.²⁰ *Id.* at 2. Patent Owner's point is that Petitioner's reliance on the prior art's mere teaching of a 5-azacytidine tablet having a sugar coating is insufficient to teach a tablet with a non-enteric coating as claimed.

At this stage of the proceeding, these are the themes and foundational points of the parties' arguments.

1. Anticipation by Ionescu (Ground 1)

Petitioner's Ground 1 asserts that claims 1, 2, 6–8, 11, 13–18, 20–23, 28, 32–35, 38, 40, 42, and 43 are anticipated by Ionescu. *See* Pet. 6, 20–31 (citing, concerning independent claims 1 and 28, Ex. 1001, 10:43–48, 11:42–48, 37:38–38:6, 40:38–41, 82:21–23 (claim 13), 82:61–83:2 (claim 28), claims 8, 9, 16, 17, 23–27, 35, 36; Ex. 1004, Abstract, 1:10–11, 1:28–32, 2:26–28, 5:12–14 12:13–14:7; 14:18–29).

Independent Claim 1

Independent claim 1 is recited in the '628 patent (Ex. 1001) at 81:55–58. We first review Petitioner's assertions.

Petitioner asserts that Ionescu discloses claim 1's preamble's subject matter [1a] (if it is considered a limitation), “[a] *pharmaceutical composition for oral administration comprising*,”²¹ because Ionescu discloses 5-azacytidine made into dosage units, for example, tablets, for oral

²⁰ Patent Owner also asserts that we should deny institution here based on our discretion under 35 U.S.C. § 325(d). We address this issue below at Section III.

²¹ Claim language italicized here and throughout for emphasis.

use. Pet. 21 (citing Ex. 1004, Abstract, 12:17–25, 13:11–12, 13:19–14:7, 14:18–28).

Petitioner asserts Ionescu discloses limitation [1b], “*a therapeutically effective amount of 5-azacytidine*,” because Ionescu discloses dosage amounts of 5-azacytidine sufficient to provide a therapeutic benefit for the disease/disorder (for example MDS), provided, for example, in unit dosage form (e.g., about 5–200 mg) for humans or mammal patients. *Id.* at 21–22 (citing Ex. 1001, 1:10–11, 10:43–48, 14:22–29).

Petitioner asserts that Ionescu discloses limitation [1c], “*at least one pharmaceutically acceptable excipient*,” because Ionescu discloses including in unit dosage forms a pharmaceutically acceptable carrier, diluent, or excipient. *Id.* at 22 (citing Ex. 1004, 2:26–28, 12:13–13:27, 14:25–29).

Petitioner asserts that Ionescu discloses the final limitation [1d], “*wherein the composition is a non-enteric coated tablet*,” because Ionescu disclose its tablets may be coated with a concentrated solution of sugar and may provide quick release of the drug upon administration. *Id.* at 22 (citing Ex. 1004, 13:7–10, 13:16–18). Petitioner asserts that Ionescu’s 5-azacytidine tablets’ sugar coatings would be quickly dissolved in the stomach and would not be intended for releasing the drug beyond the stomach and, thus, satisfy the “non-enteric coated” limitation in that they provide “a pharmaceutical composition, formulation, or dosage form that does not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine).” *Id.* at 22–23 (citing Ex. 1001, 11:42–48, 40:38–41, 82:21–23); *see also supra* Section II.B (construction of “non-enteric coated”).

We now turn to Patent Owner’s arguments and evidence in response.

Patent Owner's statements, arguments, and evidence presented in its Preliminary Response confirm that, as asserted by Petitioner, Ionescu discloses the pharmaceutical 5-azacytidine, that this drug treats diseases such as MDS, that it may be formulated as a tablet (for oral delivery) with an excipient, and that a 5-azacytidine tablet may be sugar-coated (a common type of tablet coating). Prelim. Resp. 20–21, 28, 31; *see also* Ex. 2001 ¶¶ 37–39, 49 (Dr. Berkland discussing Ionescu's disclosure, confirming the same). Patent Owner argues over none of these facts (nor does Patent Owner argue whether Ionescu is an enabling disclosure for the purposes of anticipation).

Patent Owner argues that Ionescu's disclosure of a sugar-coated tablet does not disclose “a non-enteric coated tablet” as required by all claims. Prelim. Resp. 25. Patent Owner argues that the evidence supports that sugar coatings are not drug-release control coatings, but serve to protect the drug from the environment and are used for aesthetics. *Id.* at 26–28 (citing Ex. 2001 ¶¶ 50–51; Ex. 1006, 62, 72; Ex. 1030, 9, 47). Patent Owner further argues that sugar coatings are not necessarily non-enteric and may be enteric coatings if their first sealing coat is so engineered, e.g., “additional quantities of seal-coat solution are applied”—quoting Remington (Ex. 1030). *Id.* at 28–31 (citing Ex. 2001 ¶¶ 52–56, 58; Ex. 1004, 12:7–13:21; Ex. 1006, 63, Fig. 11.24; Ex. 1030, 47, 49–50; Ex. 2020, 79–80, 83; Ex. 2028, 889, 930–31).

A second prong of Patent Owner's argument over Ionescu's alleged anticipation is that, even considering the inclusion of a sugar-coating in the reference's 5-azacytidine tablets, a person of ordinary skill in the art reading the reference would have understood that these were enterically coated

tablets (even without any specific reference to such a property). *Id.* at 32–37. Patent Owner’s rationale for this position is that the “degradation challenges,” i.e., acidic instability and enzymatic degradation, relating to 5-azacytidine were established; thus, an ordinarily skilled artisan developing an oral tablet for this drug, seeking to avoid this degradation in the stomach, would have understood a sugar coating disclosed in a reference to be the enteric variant to prevent exposure of the drug until after passing the stomach. *Id.* (citing Ex. 2001 ¶¶ 57, 64–85; Ex. 1002 ¶¶ 55, 119; Ex. 1003 ¶¶ 27, 34–35; Ex. 1014; Ex. 1021; Ex. 1034; Ex. 2003; Ex. 2004; Ex. 2011; Ex. 2012; Ex. 2016; Ex. 2017; Ex. 2019; Ex. 2021; Ex. 2022; Ex. 2023; Ex. 2024; Ex. 2027; Ex. 2029; Ex. 2034; Ex. 2041; Ex. 2043; Ex. 2047).

Having considered the arguments and evidence at this stage of the proceeding, we find that Patent Owner appears to have pointed out a problem with Petitioner’s case for Ionescu’s anticipation of claim 1.

Petitioner has accounted for all elements of claim 1 as disclosed by Ionescu, for the reasons noted above in summarizing the Petition. That is, it is undisputed that Ionescu teaches a composition of a therapeutically effective amount of 5-azacytidine for oral administration, with a pharmaceutically acceptable excipient. The only issue in dispute at this stage of the proceeding is whether Ionescu’s tablet is “a non-enteric coated tablet.” Based on our claim construction of this term (*see supra* Section II.B), a tablet without an enteric coating would satisfy the disputed claim limitation. Although Ionescu *appears* to disclose such an uncoated tablet (*see, e.g.*, Ex. 1004, 12–14), in our reading of the Petition, Petitioner does not make this case and solely points to the Ionescu embodiment having an optional sugar coating as definitively being a non-enteric coated tablet (*see*

Pet. 22–23).²² Based on the evidence of record at this stage of the proceeding, we cannot agree that mere disclosure of a sugar coating necessarily means the tablet is a non-enteric coated tablet. We explain below.

Both parties focus on the fact that Ionescu states,

In certain embodiments of the invention, the ***5-azacytidine forms(s) may be made into the form of dosage units for oral administration.*** . . . The mixture is then ***pressed into tablets*** or filled into capsules. ***If coated tablets***, capsules, or pulvules are ***desired, such tablets***, capsules, or pulvules ***may be coated with a concentrated solution of sugar . . .***”

Ex. 1004, 13 (emphasis added); *see also* Pet. 20–23; Prelim. Resp. 25–37.

At this point, we agree with Patent Owner that the evidence supports it is possible for a tablet’s sugar coating to be made enteric, as this is expressly stated by Remington. Ex. 1030, 47.

Petitioner does not assert that Ionescu expressly states that its tablets are non-enteric coated tablets. *See* Pet. 22–23. Instead, Petitioner states:

Ionescu discloses that its pharmaceutical compositions of 5-azacytidine may be a NEC tablet, specifically a tablet “coated with a concentrated solution of sugar[.]” (*Id.* at 13:16-18.) At least the sugar-coated tablets of Ionescu are NEC and “provide quick . . . release of the drug substance after administration to the patient.” (*Id.* at 13:7-10.)

The ’628 patent defines “non-enteric-coated” as “a pharmaceutical composition, formulation, or dosage form that does not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine).” (EX-1001 at 11:42-48.) Sugar coatings, like those of Ionescu, are quickly dissolved in the low pH conditions of the stomach, and

²² We also recognize that Dr. Buckton states that “it would be unusual for tablet dosage forms to lack a film coating as of the priority date. (EX-1006, Gibson at 433 [62]; EX-1030, Remington at 894.)” *See* Ex. 1002 ¶ 46.

are not intended to release significant amounts of 5-azacytidine beyond the stomach. (*See id.* at 40:38-41.) This use of sugar coatings as a NEC is confirmed by Claim 13 of the '628 patent, which depends from Claim 1 and further recites “a sugar coating” as one type of NEC. (*Id.* at 82:21-23.)

Id. Relatedly, Petitioner also states,

Ionescu (EX-1004), for example, teaches NEC tablets of 5-azacytidine, i.e., tablets that “do[] not comprise a coating intended to release the active ingredient(s) beyond the stomach (e.g., in the intestine).” (EX-1001 at 11:42-48.) *Specifically, Ionescu teaches that pharmaceutical compositions of 5-azacytidine may comprise sugar-coated tablets.* (EX-1004 at 13:16-19.) At a minimum, the sugar-coated tablets of Ionescu are NEC and “provide quick . . . release of the drug substance after administration to the patient.” (*Id.* at 13:7-10.)

Id. at 11 (emphasis added). Thus, it is our understanding that Petitioner relies on an inherent anticipation theory that Ionescu’s tablet’s sugar coating is necessarily a non-enteric coating.

“A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference.” *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). However, “[i]nherency . . . may not be established by probabilities or possibilities.” *In re Montgomery*, 677 F.3d 1375, 1379–80 (Fed. Cir. 2012) (citations omitted, alterations in original). “The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency.” *Scaltech Inc. v. Retec/Tetra L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999).

The evidence at this preliminary stage supports that, generally, sugar coatings are *not* enteric coatings and are distinguished therefrom, where enteric coatings are typically satisfied using a film coating. *See Ex. 1006*,

62–72, Table 11.18; Ex. 1030, 853, 895–99; Ex. 2028, 889–90, 930–33. For example, Gibson, when introducing sugar and film coatings, is explicit that, when referring to generic sugar or film coatings, the “coat should not delay the release of the drug substance from the tablet” and that “[i]t is possible to design a coat that will modify the release of a drug substance for a beneficial effect,” but for that Gibson points to film coatings, not sugar coatings. Ex. 1006, 68–70; *see also* Ex. 2020, 80 (suggesting that, by default, tablet sugar coatings are non-enteric and stating “if the final product is to have enteric properties, this result is usually achieved by using one of the enteric polymers (such as PVAP or CAP) as the basis for the seal coat and ensuring that sufficient coating material is applied”).

However, this general understanding that sugar coatings are not enteric coatings is modified by other evidence of record, which teaches that “[i]f an enteric-coated product is required,” a sugar coating can satisfy this need if “additional quantities of the seal-coat [of the sugar-coating] are applied.” Ex. 1030, 895. For this reason, we cannot agree with Petitioner that mere disclosure of a sugar-coated tablet is necessarily disclosure of a non-enteric coated tablet so as to inherently anticipate such a claim limitation. We discern no other rationale supplied by Petitioner for Ionescu’s anticipation of claim 1’s limitation [1d], “*wherein the composition is a non-enteric coated tablet.*” For this reason, based on our understanding of Petitioner’s arguments, we cannot find that there is a reasonable likelihood that Petitioner will prevail in proving Ionescu anticipates independent claim 1.

Independent Claim 28

Independent claim 28 is recited in the '628 patent at (Ex. 1001) 82:61–83:2. It defines “[a] method for treating one or more symptoms of a disease associated with abnormal cell proliferation,” like MDS, by “orally administering to a subject in need thereof” the same pharmaceutical composition of 5-azacytidine in “a non-enteric coated tablet” as set forth in claim 1 (and requires that the treated disease is MDS or AML). *Id.* Thus, claim 28 is directed to using the tablet of claim 1 for treatment.

Petitioner asserts that, as to all the elements/limitations of claim 28 that mirror those of independent claim 1, the same disclosures of Ionescu meet those limitations. Pet. 23. As to the limitations of claim 28 that are different than claim 1, Petitioner asserts that the preamble, “[a] method for treating one or more symptoms of a disease associated with abnormal cell proliferation,” and the further narrowing of this disease, “wherein the disease associated with abnormal cell proliferation is [MDS] or [AML],” is disclosed by Ionescu where it identifies 5-azacytidine is used in the treatment of MDS. *Id.* (citing Ex. 1004: 1:10–11, 1:28–32, 5:12–14).

At this stage of the proceeding, Patent Owner argues the patentability of independent claims 1 and 28 over Ionescu together, without differentiating between the two claims. Prelim. Resp. 25–37.

We find that, for the same reasons stated above for independent claim 1, we cannot find there is a reasonable likelihood that Petitioner will prevail in proving Ionescu anticipates independent claim 28.

Dependent Claims 2, 6–8, 11, 13–18, 20–23, 32–35, 38, 40, 42, and 43

Claims 2, 6–8, 11, 13–18, 20–23 each depends directly or indirectly from independent claim 1, and dependent claims 32–35, 38, 40, 42, 43 each

depends from independent claim 28. Ex. 1001, 81:59–82:52, 83:12–84:23. These claims recite additional components included in the tablet, certain compounds that must be omitted or not co-administered with 5-azacytidine, a variety of dosages or ranges of doses for 5-azacytidine, pharmacokinetic results from administering the tablet to a test subject, certain coatings included in the tablet, and that the composition is a unit dosage form. *Id.* However, each dependent claim requires the non-enteric coated tablet of independent claims 1 or 28 and, therefore, we cannot find Petitioner shows a reasonable likelihood of prevailing at trial in proving Ionescu anticipates any of these dependent claims.

2. *Obviousness Over Ionescu, Atadja, Gibson, and Pharmion-PR (Grounds 2 and 3)*

Under Grounds 2 and 3, Petitioner asserts that claims 1, 2, 6–9, 11–28, 32–36, and 38–43 would have been obvious over Ionescu, Atadja, and Gibson, with Ground 3 adding the Pharmion-PR reference to this prior art combination.²³ Pet. 6, 30–62. There is no dispute at this stage of the proceeding that Pharmion-PR is prior art. *See generally* Prelim. Resp.; *see also supra* Section II.D (summarizing the asserted prior art). Thus, Ground 2 is subsumed by Ground 3 and, so, we will address the two obviousness grounds together and will include the Pharmion-PR reference in our preliminary analysis.

Petitioner cites the same disclosures of Ionescu under its obviousness grounds as cited under its anticipation ground. Pet. 31–32; *see supra* Section II.E.1. Thus, it is again Ionescu’s sugar-coating to which Petitioner

²³ As compared to anticipation Ground 1, these Grounds add dependent claims 9, 12, 19, 24, 25, 26, 27, 36, 39, and 41.

points as rendering obvious the disputed claim 1 limitation [1d], “*wherein the composition is a non-enteric coated tablet.*” Pet. 31–32 (referring to *id.* at 21–23).

Petitioner adds Atadja (Ex. 1005) for its teaching of administering the same drug, 5-azacytidine, to treat the same types of conditions (abnormal cell proliferation), also using orally administered tablets, like Ionescu, but further for Atadja’s disclosure of formulations without cytidine deaminase inhibitors like THU (claims 6, 7, 32) to bolster Ionescu’s similar omissions, for its teaching and suggested optimization of certain dosages of 5-azacytidine (claims 8, 9, 16, 23–27, 35, 36), for its teaching of a *single unit dosage form* to bolster Ionescu’s similar disclosure (claim 33), to support the inherency of certain claimed PK results based on administered doses of 5-azacytidine (claims 11, 12, 18–22, 38–43), and to support a reasonable expectation of success in making and using the claimed invention. Pet. 39, 44–45, 47–51, 60–61.

Petitioner adds Gibson (Ex. 1006) for its teachings directed to the benefits of pharmaceutical oral dosage forms and NEC tablets and their being “the default” choice and “most preferred dosage form” relative to enteric coated variants, for its disclosure regarding methods of making such tablets, as support that making Ionescu’s 5-azacytidine non-enteric coated tablet would have been obvious to try, for its disclosure of sugar and film coatings and materials used therefore (claims 13–15), and as support for a reasonable expectation of success in making the invention using conventional methods. Pet. 31–31, 33, 35–38, 41–43.

Petitioner further adds Pharmion-PR (Ex. 1010) as providing further motivation for the ordinarily skilled artisan to modify Ionescu’s teachings

and combine it with Atadja and Gibson with a reasonable expectation of success to achieve the claimed invention (claims 1, 28), for Pharmion-PR's teaching of clinical studies of orally administered 5-azacytidine to treat MDS (claims 1, 28), for its teachings that this formulation of the drug was well-tolerated by and bio-available to patients, of the advantages of an oral administration, of the relative bio-availability of the oral 5-azacytidine dose compared to an SC administration of the approved Vidaza drug so as to motivate dosage optimizing (claims 8, 9, 16, 17, 23–27, 35, 36), and for teaching *single unit doses* (claim 33). Pet. 58–62.

Petitioner asserts there would have been good reason for the ordinarily skilled artisan to have combined Ionescu, Atadja, Gibson, and Pharmion-PR because, *inter alia*, they are all directed in some way to oral pharmaceutical formulations for treating proliferative diseases with oral 5-azacytidine (all but Gibson, which is more general in nature), and one reference would inform a reader of another as to, for example, useful and optimized doses of the drug, conventional ways of making tablets, the advantages of coatings, and the tolerability and bioavailability of the drug in oral dosages. *Id.* at 31–35, 59–61.

Moreover, Petitioner asserts that, based on the teachings of these references, the person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention because, *inter alia*, non-enteric coated tablets were a default form that would be tried first, 5-azacytidine had been shown to be orally bioavailable to and well tolerated by patients, coated tablets are simple and predictable to manufacture and the process was well-documented by Gibson, and a wide range of doses of 5-azacytidine were taught and routine optimization thereof

suggested and directed by Atadja and Pharmion-PR. *Id.* at 32, 36, 38, 41–48, 61–62.

We next address Patent Owner’s arguments on the obviousness grounds.

The foundation for Patent Owner’s arguments is not very different from its arguments over anticipation by Ionescu: *a sugar coating is not necessarily a non-enteric coating*. Prelim. Resp. 38. Patent Owner also argues that Petitioner fails to show that the ordinarily skilled artisan would have had a reasonable expectation of success. Prelim. Resp. 40–46. On this, Patent Owner’s points are that Petitioner’s case disregards the (undisputed) known instability of 5-azacytidine and that, in view of this characteristic of the drug, the person of ordinary skill in the art would not have tried developing or administering an oral formulation of 5-azacytidine without a protective enteric coating. *Id.* (citing, *inter alia*, Ex. 2001 ¶¶ 48–57, 59–85).

At this stage of the proceeding we are not persuaded by Patent Owner’s arguments and find Petitioner’s case sufficient to show it reasonably likely to succeed at trial on its obviousness grounds. We explain below.

The evidence supports that Patent Owner is correct that, before the ’628 patent, 5-azacytidine was thought to be unstable in an acidic environment (like the stomach); the ’628 patent expressly makes this point and indicates it was an obstacle to providing oral delivery of the drug. Ex. 1001, 3:54–58; *see also* Pet. 15 (noting this same disclosure without contesting its accuracy). We remain uncertain, however, about just how severe of a perceived obstacle this instability may have been, based, *inter alia*, on the fact that the remainder of the ’628 patent’s written description

never explains what the inventors specifically did to overcome the problem. *See generally* Ex. 1001.

Moreover, there is substantial evidentiary support that those in the relevant field were developing orally administered 5-azacytidine, both with and without enteric coatings. For example, Ionescu discloses a variety of orally delivered 5-azacytidine formulations such as capsules, tablets, lozenges, and syrups. Ex. 1004, 12–14. In our understanding of the technology, there is no way to control the release of the drug from a lozenge or syrup so as to bypass the stomach nor would such formulations be used if stomach bypass was desired, which suggests Ionescu is unconcerned with controlled or delayed drug release as most of these formulation types do not provide such control. *See* Pet. 37 (citing Ex. 1004, 12:17–27; Ex. 1005, 27; Ex. 1002 ¶¶ 127–128). Further, Ionescu discloses that when 5-azacytidine is formulated in a tablet or capsule, such tablets/capsules may or may not be coated, as desired. Ex. 1004, 13–14. If coated, Ionescu discloses a sugar-coating and the evidence of record supports that, generally, sugar coatings are *not* enteric coatings and are typically distinguished therefrom, where enteric coatings are typically satisfied using a film coating. *See* Ex. 1006, 62–72, Table 11.18; Ex. 1030, 853, 895–99; Ex. 2028, 889–90, 930–33. Again, Gibson, when introducing sugar and film coatings, is explicit that, when referring to generic sugar or film coatings, the “coat should not delay the release of the drug substance from the tablet” and that “[i]t is possible to design a coat that will modify the release of a drug substance for a beneficial effect,” but for that Gibson points to film coatings, not sugar coatings. Ex. 1006, 68–70; *see also* Ex. 2019–20, 80 (suggesting that, by default, tablet sugar coatings are non-enteric and stating “if the final product is to

have enteric properties, this result is usually achieved by using one of the enteric polymers (such as PVAP or CAP) as the basis for the seal coat and ensuring that sufficient coating material is applied.”). Although, as noted above, the evidence of record shows that “[i]f an enteric-coated product is required,” a sugar coating *can* satisfy this need if “additional quantities of the seal-coat [of the coating] are applied” (Ex. 1030, 895), we find the other evidence of record noted above supports that it would have been obvious for Ionescu’s sugar-coating to be non-enteric. Nothing in Ionescu suggests a desire for controlled drug release that would require specially modifying the optional sugar-coating to be enteric.

Atadja also discloses an oral pharmaceutical formulation of 5-azacytidine as a tablet, capsule, or syrup—this again contemplates uncontrolled drug delivery in our understanding of the technology. Ex. 1005, 27. Pharmion-PR is non-specific about the formulation of its orally delivered azacytidine, but, nonetheless, the reference discloses clinical uses of the drug orally with some degree of success. Ex. 1010. Vorbruggen very generally discloses an oral dosage of 5-azacytidine. Ex. 1016, 1:4–18, 4:52–53. Sands discloses an oral formulation of 5-azacytidine as a tablet or capsule with an enteric coating. Ex. 1021 ¶¶ 29, 34, 36, 39, 40. Dover discloses work in developing an optimal oral regimen of 5-azacytidine based on prior animal testing (apparently with limited success). Ex. 1031, 527–28. Stoltz (published in 2006) reports on the success of Pharmion Corporation’s efforts at developing an oral dosage of azacytidine in spite of the known hydrolytic instability and enzymatic degradation challenges. Ex. 1034. Ward reports in 2007 that oral azacytidine was preclinically tested with dogs to develop a dosing strategy and that, based on such, a multicenter clinical

test or orally administered azacytidine for patients with MDS, AML, or solid tumors was underway. Ex. 2040. All this undermines Patent Owner’s insistence that mere oral delivery of 5-azacytidine indicates a requirement for an enteric coating and, rather, supports Petitioner’s position that Ionescu’s sugar-coated tablet teaches a non-enteric coated tablet.

In view of this evidence, we are unpersuaded by the entirety of Patent Owner’s preliminary arguments that ordinarily skilled artisans would have neither been motivated to make a non-enteric coated tablet of 5-azacytidine nor would have lacked a reasonable expectation for success in doing so. We find, on balance at this stage, the evidence supports that Petitioner shows a reasonable likelihood of prevailing at trial as to at least one claim under Ground 3.

III. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Petition presents substantially the same art and arguments that the Office previously analyzed and fails to show that the Office erred during prosecution. *See* Prelim. Resp. 46–68.

We have discretion to deny institution when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d) (“Section 325(d)”). In that respect, Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.²⁴ *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte*

²⁴ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

GmbH, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating the exercise of discretion to deny institution under Section 325(d), the Board uses the following two-part framework:

- (1) [determining] whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
- (2) if either condition of [the] first part of the framework is satisfied, [determining] whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, Paper 6 at 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”).

Becton, Dickinson Factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. *Becton, Dickinson* Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* “At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9.

A. WHETHER THE SAME OR SUBSTANTIALLY THE SAME ART OR ARGUMENTS WERE PREVIOUSLY BEFORE THE OFFICE

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. The prosecution history of the ’628 patent is of record here as Exhibit 1022.

Patent Owner asserts that Ionescu, as well as several other references cumulative of Ionescu, were submitted to and considered by the Examiner during the prosecution of the ’628 patent. Prelim. Resp. 46, 50–55. Patent Owner points to an international search report citing a foreign/international relative application of Ionescu and, specifically citing to portions thereof that mirror the most relevant parts of Ionescu to this proceeding, to support an

argument that the Examiner considered or made some express argument over Ionescu. *Id.* at 53 (citing Ex. 1022, 634 (ISR dated Sept. 14, 2009)).

Patent Owner argues that Atadja, while not before the Examiner, is so generic as to the relevant subject matter that it is cumulative to other prior art that was of record during prosecution and cited against pending claims in Examiner rejections. *Id.* at 55–56 (citing Ex. 1022, 644–55, 1072–83, 2015–25 (Office Actions); Ex. 2033 (disclosing azacytidine oral tablets, capsules, and syrups); Ex. 1019 (disclosing 5-azacytidine oral formulations in the form of tablets, capsules, suspensions, and liquids); Ex. 1021 (disclosing 5-azacytidine compositions as tablet or capsule)).

Patent Owner argues Gibson was before the Examiner as cited within the '628 patent's Specification. *Id.* at 56 (citing Ex. 1001, 37:24–32).

Patent Owner argues Pharmion-PR was not before the Examiner, but is cumulative to references that were. *Id.* at 57–58 (citing Ex. 2040 (disclosing an oral dosage of azacytidine and a PK study, as well as a clinical study underway); Ex. 2041 (disclosing oral dosage of 5-azacytidine enteric tablets, as well as a clinical study of MDS, AML, and solid tumor patients)).

It is undisputed that Ionescu was of record and before the Examiner during prosecution of the '628 patent. Pet. 62 (Petitioner concedes this).

Petitioner argues that Gibson was not before the Examiner; however, we disagree because, as pointed out above, Gibson was expressly cited in the Specification of the '628 patent for its disclosure of “conventional methods known to those skilled in the field of pharmaceutical formulation.” Ex. 1001, 37:20–32.

Petitioner argues that Atadja and Pharmion-PR were not of record and before the Examiner. *Id.* This Patent Owner concedes, while arguing they are cumulative. *See above.*

With respect to Atadja, Petitioner cites the reference, in part, as support that delayed drug release for 5-azacytidine was not an insurmountable concern in the prior art and for its disclosure of dosages of 5-azacytidine to be used for oral administration. *See, e.g.,* Pet. 37, 44–46. Patent Owner does not identify why such teachings of Atadja would be cumulative over the prior art noted above that was of record during prosecution. Thus, we are not convinced it is cumulative.

As to Pharmion-PR, Petitioner cites the reference, at least in part, as evidence that oral 5-azacytidine was *well tolerated* by human patients to support the position that the ordinarily skilled artisan would have been *motivated* to develop such an oral formulation. Pet. 60. We do not discern from Patent Owner’s position that this is part of the other cited prior art and are not convinced Pharmion-PR is cumulative for at least this reason.

Thus, half the asserted prior art, Ionescu and Gibson, were before the Office during prosecution of the ’628 patent and half, Atadja and Pharmion-PR, were not. However, concerning Petitioner’s Ground 1 for anticipation, the sole asserted reference, Ionescu, was before the Office. Therefore, we turn now to consider the second assessment under *Advanced Bionics*.

B. WHETHER PETITIONER HAS DEMONSTRATED THAT THE OFFICE
ERRED IN A MANNER MATERIAL TO PATENTABILITY

Petitioner asserts that, “[w]hile the Examiner correctly rejected the claims as anticipated or obvious in his first three office actions, he erred by overlooking Ionescu or misapprehending its disclosures, and was led astray by the Applicants’ erroneous arguments regarding purported unexpected

results.” Pet. 16 (citing to various parts of Ex. 1022 (prosecution history)). Further, “the Examiner never applied Ionescu to reject the pending claims even though Ionescu plainly teaches NEC (specifically, sugar-coated) tablets of 5-azacytidine.” *Id.* at 17.

Patent Owner argues that there was no such error because, mirroring its arguments concerning patentability, “Ionescu does **not** disclose non-enteric coated tablets of 5-azacytidine.” Prelim. Resp. 47, 59–61 (emphasis Patent Owner’s).

We agree with Petitioner. Had the Examiner considered Ionescu, as we have here, in view of the claims that issued in the ’628 patent and in light of the correct claim interpretation of “non-enteric coated tablet” (*see supra* Section II.B), the Examiner would have cited Ionescu against the claims so as to require the Applicant to respond and distinguish or amend the claims thereover. This the Examiner did not do and we agree with the Petitioner that this was an error material to the patentability of the claims.

Moreover, the critical claim language at issue in this proceeding, “a non-enteric coated” tablet, and a new claim directed to, *inter alia*, the tablet comprising a sugar coating, were added by the Applicant in its final Office Action Response, just before allowance and issuance of the claims, which were not challenged by the Examiner in any rejection. *See* Ex. 1022, 2062–84 (February 27, 2014 Response). The Applicant pointed out this amended claimed subject matter as new. *Id.* Applicant argued in that Response that “[a] novel and unique element of the claimed composition is the absence of an enteric coating, *i.e.*, a coating that is designed to release the active ingredient beyond the acidic environment of the stomach when orally administered.” *Id.* at 2072–73. Further, the Applicant argued at length that

the prior art asserted by the Examiner as rendering the claims obvious failed in that regard because the references required an enteric coated tablet. *Id.* at 73–79. Following this Response, the Examiner immediately allowed the claims, which issued as the claims challenged here, without discussing the newly added claimed subject matter. *Id.* at 2135–40.

As noted by Patent Owner, sometimes an Examiner’s mere silence on prior art cannot be taken as a material error; however, here we find reasonable minds cannot differ as to the importance of Ionescu’s disclosure as prior art with respect to the claims of the ’628 patent. *Advanced Bionics*, Paper 6 at 8–10; *see Becton, Dickinson*, Paper 8 at 24. As asserted by Petitioner, the Examiner’s failure to address Ionescu was material error.

C. CONCLUSION AS TO SECTION 325(d)

For the reasons set forth above, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. CONCLUSION

Petitioner demonstrates a reasonable likelihood of prevailing at trial in showing that at least one of claims 1, 2, 6–9, 11–28, 32–36, and 38–43 of the ’628 patent is unpatentable over the cited prior art. Our decision derives from our review of the preliminary record before us. Accordingly, we institute *inter partes* review of each challenged claim the ’628 patent on each of the grounds asserted by Petitioner. This decision does not reflect a final determination on the patentability of the claims.

ORDER

Accordingly, it is hereby:

ORDERED that the Petition is granted and we institute *inter partes* review of claims 1, 2, 6–9, 11–28, 32–36, and 38–43 of the '628 patent based on the grounds asserted in the Petition.

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Patent 8,846,628 B2

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