

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner

Case IPR2023-00512
Patent 8,846,628

EXPERT DECLARATION OF CORY BERKLAND, PH.D.

CELGENE 2051
APOTEX v. CELGENE
IPR2023-00512

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I, Cory Berkland, Ph.D., declare as follows:

I. INTRODUCTION AND BACKGROUND

1. I have been retained by counsel for Celgene Corporation (“Patent Owner”) as an expert in *Apotex Inc. v. Celgene Corporation*, No. IPR2023-00512, challenging claims 1, 2, 6-9, 11-28, 32-36, and 38-43 of U.S. Patent No. 8,846,628 (“the ’628 patent”).

2. I understand that Apotex Inc. (“Apotex”) have filed an Inter Partes Review (IPR) at the USPTO challenging claims 1, 2, 6-9, 11-28, 32-36, and 38-43 of the ’628 patent.

A. Qualifications and Experience

3. I am currently a Professor of Pharmaceutical Chemistry and a Professor of Chemical and Petroleum Engineering at The University of Kansas. I also have an appointment as a courtesy professor in the Chemistry Department at The University of Kansas. I also assisted in designing the BioEngineering graduate program at The University of Kansas, and I am the former director of the Biomolecular Engineering track within the BioEngineering program.

4. I teach courses to undergraduate and graduate students at The University of Kansas on, among other things, pharmaceutical formulation (including solid oral dosage forms), drug delivery, dissolution methods, and modeling dissolution profiles.

5. I received a Doctor of Philosophy degree from the University of Illinois in 2003 and a Master of Science degree from the University of Illinois in 2001, both from the Department of Chemical and Biomolecular Engineering. I received a Bachelor of Science degree in Chemical Engineering from Iowa State University in 1998.

6. I have worked in the area of pharmaceutical formulation for over 20 years. A significant portion of my career has been dedicated to the study of formulating therapeutics for delivery to patients. I currently research the design of molecules and materials specialized for a particular disease and targeted drug delivery to maximize their therapeutic effect while limiting side-effects. I have extensive experience in the area of pharmaceutical delivery design including preformulation, formulation, analysis, and related theories.

7. I have published over 200 peer-reviewed papers, and I have presented my research at many national and international research conferences and to companies, including more than 75 invited talks. I have also given distinguished lectures such as the Nagai Foundation Distinguished Lectureship in Japan and a lectureship at the Center of Excellence in Nanotechnology at the Massachusetts Institute of Technology. I also serve or have served on the editorial advisory board for a number of peer-reviewed journals: Therapeutic Delivery, The Journal of Pharmaceutical Sciences, and The Journal of Pharmaceutical Innovation. I also

serve or have served on advisory boards for the Center for Cancer Engineering at The Ohio State University, the Drug Discovery and Development of Experimental Therapeutics program, and the National Institutes of Health Pharmaceutical Aspects of Biotechnology training grant program at The University of Kansas.

8. I have received funding for my research from the National Institutes of Health including the National Cancer Institute, the National Science Foundation, the Department of Defense, the Defense Threat Reduction Agency, the PhRMA Foundation, the Coulter Foundation, the American Heart Association, the Cystic Fibrosis Foundation, the Juvenile Diabetes Research Foundation, several other philanthropic organizations, and multiple pharmaceutical companies.

9. Over the years I have been an active participant in a number of professional societies including the American Institute of Chemical Engineers, the Controlled Release Society, the American Chemical Society, and the American Association of Pharmaceutical Scientists. I have also been elected Fellow of the American Institute for Medical and Biological Engineering and was elected to the National Academy of Inventors.

10. I have received numerous awards in recognition of my research, including the Controlled Release Society Young Investigator Award and the Coulter Translational Research Award. At the University of Kansas, I have received major research awards such as the University Scholarly Achievement

Award, the Jim Baxendale Commercialization Award, the Leading Light Award, and the Miller Professional Development Award for Research, and I was named a Bellows Scholar in the School of Engineering at The University of Kansas. I have also received the W.T. Kemper Fellowship for teaching excellence at The University of Kansas.

11. I have been granted multiple patents and have co-founded seven companies: Bond Biosciences, Exodus Biosciences, Orbis Biosciences (acquired by Adare Pharmaceuticals), Kinimmune, Orion BioScience, Axioforce, and Savara Pharmaceuticals. I have held executive positions at each of these companies. I am currently the Chief Executive Officer and Chairman of the Board of Directors at Bond Biosciences. I am also currently the Chief Executive Officer and Chairman of the Board of Directors at Kinimmune.

12. I have worked as a consultant in the pharmaceutical industry providing formulation advice to multiple major pharmaceutical and biotechnology companies. I also worked at a biotechnology investment firm, Sofinnova Ventures, during a six-month sabbatical in 2014.

13. Overall, I have about 20 years of experience designing therapeutic formulations and testing their release profiles. In my work described above, I have performed formulation delivery testing many times on oral solid dosage forms, for example, tablets, powders, capsules, and suspensions. I have performed analysis

of release profiles for delivery of therapeutics, for example, in my research work at The University of Kansas. This includes analysis of both controlled and immediate release formulations.

14. I have conducted many comparative dissolution studies in my work described above. Much of this work has been optimizing formulations for either immediate or extended release, for example, in my work consulting for pharmaceutical companies in connection with FDA filings for pharmaceutical products and in my research.

15. I have, on many occasions, designed and optimized solid oral dosage forms, including tablets, powders, capsules, and suspensions, for example, in my work at Orbis Biosciences.

16. My curriculum vitae, which lists my professional experience and qualifications in greater detail, is attached hereto as **Appendix A**.

B. Compensation

17. I am being compensated at my normal consulting rate for my work, which is \$750 per hour. My compensation is not dependent on the outcome of this matter, and it in no way affects the substance of my opinions in this Declaration.

II. LEGAL PRINCIPLES

18. The opinions I express in this Declaration involve the application of my technical knowledge and professional experience to the evaluation of certain

art with respect to the '628 patent. Because I am not an attorney, I have applied the following legal principles explained to me by Patent Owners' legal counsel ("counsel").

A. Claim Construction

19. For the purposes of this Declaration, I understand that certain principles of law are relevant to my analysis and opinions. For example, I understand that before a patent validity determination can be made, the claims must be construed by the Board.

20. I understand that in an *Inter Partes* Review ("IPR"), the Board construes claim terms in light of the specification of the patent in which they appear. I further understand that a claim construction analysis begins with the ordinary meaning of the disputed claim term, and there is a presumption that claim terms carry their accustomed meaning to a person of ordinary skill in the art ("POSA"). I have also been informed that the ordinary and customary meaning of a claim term may be determined by reviewing a variety of sources, including the claims themselves, the specification (or "written description") of a patent, its prosecution history, and dictionaries and treatises.

21. I understand that the patent specification is the single best guide to the meaning of a disputed term. I understand that the intrinsic evidence, namely the patent specification and the prosecution history, may clarify whether the patentee

intended a claim term to have a meaning that is different than its ordinary and customary meaning, or clearly disavowed the ordinary meaning in favor of some special meaning. The specification may include a special definition given to a claim term by the patentee that differs from its ordinary meaning. In such cases, the inventor's lexicography governs.

22. I further understand that a patent is a fully integrated written instrument, and a skilled artisan is deemed to read the claim term in the context of both the particular claim where the disputed term appears and the entire patent, including the specification. Accordingly, it is my understanding that the specification is always highly relevant to the claim construction analysis and is the single best guide to the meaning of a disputed term.

23. I understand that extrinsic evidence, which includes expert and inventor testimony, dictionaries, and learned treatises, may also be considered during the claim construction process. However, extrinsic evidence is given less weight than the intrinsic record in determining the meaning of disputed claim terms. I understand that dictionary definitions may reflect or establish the plain and ordinary meaning of claim terms; however, when construing claim terms, reference should also be made to the intrinsic record to determine which dictionary definition(s) are appropriate in light of the use of the claim terms by the inventor.

B. Anticipation

24. I have been informed by counsel that a patent claim is invalid under 35 U.S.C. § 102 as anticipated if each element of that claim is present either explicitly or inherently in a single prior art reference. I have also been informed that, to be an inherent disclosure, the prior art reference must necessarily disclose the limitation, and the fact that the reference might possibly practice or possibly contain a claimed limitation is insufficient to establish that the reference inherently teaches the limitation. I have also been informed that, to find anticipation, each and every limitation recited in a claim must be found in one item of prior art arranged in the same way as it is claimed. I have also been informed that references that are ambiguous to the presence or description of a particular claim element cannot anticipate a claim. I have also been informed that, for anticipation, a prior art reference must clearly direct those skilled in the art to the claimed invention without any need for picking, choosing, and combining various disclosures not directly related to each other.

C. Obviousness

25. I have been informed that a patent claim is unpatentable under 35 U.S.C. § 103 as obvious if the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. I understand that the obviousness analysis involves several factual inquiries: (1) the scope and

content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art at the time of the invention; and (4) the existence of objective indicia of non-obviousness (“objective indicia”), such as a long-felt but unresolved need, the failure of others, unexpected results, and commercial success. I understand that for objective indicia to be given weight, there must be a nexus between the evidence of objective indicia and the merits of the claimed invention.

26. I have been informed that a patent claim is unpatentable as obvious if it is obvious to try. I understand that to establish a claimed invention was obvious to try, a party must establish, at the time of the invention: (1) that there was a recognized problem or need in the art, including a design need or market pressure; (2) that there was a finite number of identified, predictable solutions to the recognized problem or need; (3) that one of ordinary skill in the art could have pursued these finite, identified, and predictable solutions with a reasonable expectation of success; and (4) whatever additional facts may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

27. I understand that a petitioner in an IPR bears the burden of proving the obviousness of the claimed invention. My understanding is that obviousness is not proven by mere conclusory statements or conclusory expert testimony. Instead, I understand there must be some articulated reasoning with a rational

underpinning to satisfy the legal standard of obviousness. I understand that, for a claim to have been obvious, there must have been some reason or motivation for a POSA to modify or combine the teachings of the prior art references to achieve the claimed invention, and the POSA must have had a reasonable expectation of success in doing so. I have also been informed that it is improper to rely on hindsight reasoning in the obviousness analysis.

III. PERSON OF ORDINARY SKILL IN THE ART

28. A POSA relating to the subject matter of the '628 patent would have had (1) a Pharm.D., and/or a Ph.D. in pharmaceutical sciences, biomolecular engineering, chemical engineering, chemistry, or related discipline or an M.D.; and (2) at least two years of experience with oncology, medicine, pharmaceutical design, or formulation of oral dosage forms. As of December 2008 I would have been a POSA.¹

¹ Petitioner's experts, Drs. Buckton and Batchelor, each put forth identical definitions of a POSA. Ex.1002(Buckton Decl.), ¶17; Ex.1003(Batchelor Decl.), ¶16. They both opine that a POSA as of December 5, 2008 "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

IV. BASIS OF OPINIONS

29. In forming my opinions set forth in this Declaration, I have considered and relied on my education and experience in the fields of pharmaceutical design, formulation, development, and manufacturing of oral dosage forms. I have also relied on the materials listed in **Appendix B** and on a conversation with Dr. Jeffrey Etter, a conversation with Dr. William Blum, and a conversation with Dr. George Grass.

V. BACKGROUND

A. Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

30. I spoke with Dr. Blum, a clinician who treats patients with AML and MDS, and I have read his declaration (Ex.2053). As described in the '628 patent, I understand that acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are disorders that impact blood cells. Ex.1001('628 patent), 1:39-64. I understand that AML and MDS are serious conditions that often result in patient death. Dr. Blum explained that as of December 2008, the FDA had only approved

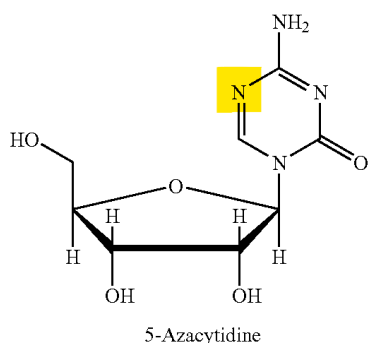
dosage forms.” Ex.1002(Buckton Decl.), ¶17; Ex.1003(Batchelor Decl.), ¶16. I qualify (and have qualified since before the priority dates of the '628 patent) as a POSA under Petitioner’s definition. My opinions would not change under Petitioner’s definition.

one oral therapy to treat MDS and no oral or maintenance therapies for AML.

Ex.2053(Blum Decl.), ¶13.

B. 5-Azacytidine

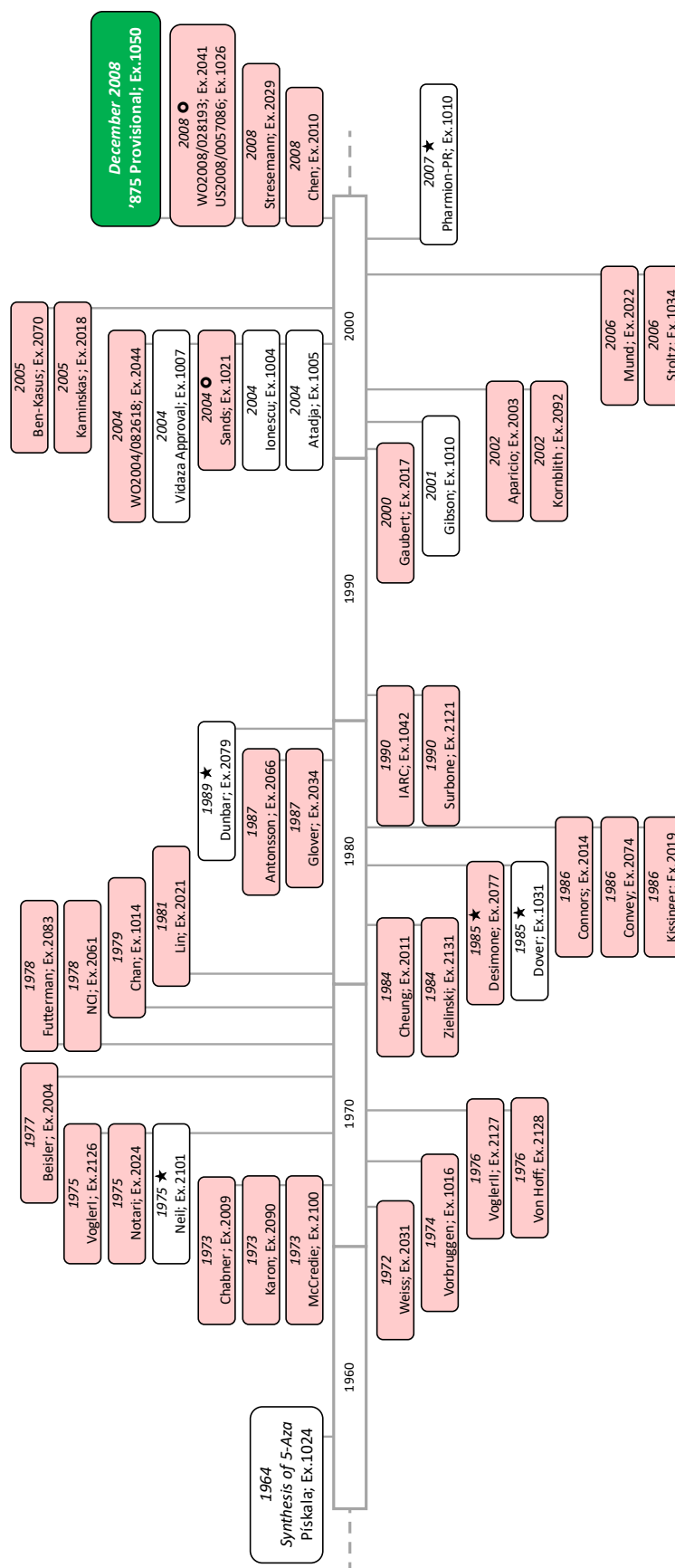
31. I have spoken with one of the inventors of the '628 patent, Dr. Jeff Etter, who worked on developing a therapeutically effective oral formulation of 5-azacytidine and I have read his declaration (Ex.2054). As described in the '628 patent, I understand 5-azacytidine is a nucleoside similar to the endogenous nucleoside cytidine, but it possesses a nitrogen atom in place of a carbon atom, which is highlighted in the structure below. Ex.1001('628 patent), 2:37-62.



Ex.1001('628 patent), 2:48-62. Once 5-azacytidine is administered, the cancer cells incorporate the 5-azacytidine into DNA and RNA. Ex.1001('628 patent), 3:9-27. I understand that upon incorporation, 5-azacytidine “restor[es] normal functions” by promoting “re-expression of genes involved in normal cell cycle regulation, differentiation and death” leading to “the death of rapidly dividing cells, including cancer cells....” Ex.1001('628 patent), 3:9-27.

C. Development History of 5-Azacytidine

32. The below figure is a timeline spanning the forty-year period between the synthesis of 5-azacytidine and the development of a therapeutically effective non-enteric tablet formulation of 5-azacytidine claimed in the '628 patent. Pink-colored entries represent publications (*e.g.*, patent applications, peer-reviewed publications, and the FDA-approved package insert for Vidaza®) that disclose that 5-azacytidine is unstable (*e.g.*, due to hydrolysis and/or enzymatic metabolism).



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

33. Researchers were interested in 5-azacytidine as an anti-cancer pharmaceutical since it was first synthesized in 1964. Ex.1024(Pi'skala). Researchers immediately recognized 5-azacytidine had the ability to halt the spread or development of cancer cells and began studying the compound's properties. *See* Ex.2116(Sorm); Ex.2012(Čihák); Ex.2027(Pit'ková); Ex.2085(Goldin). By the 1970s, researchers began administering 5-azacytidine to patients as injectable formulations in clinical trials. Ex.2128(VonHoff), 237; *see also* Ex.2088(Hrodek); Ex.2112(Shnider); Ex.2096(Lomen); Ex.2100(McCredie) (describing clinical trials of intravenous or subcutaneous formulations throughout the 1970s).

34. In 2008 a POSA would have understood that 5-azacytidine is not stable and rapidly breaks down when exposed to water. Because *in vitro* studies showed that 5-azacytidine was rapidly hydrolyzed, in clinical trials the drug had to be administered shortly after reconstitution:

- Ex.2128(VonHoff), 238, 239-240 (disclosing administering injections “within 30 min[utes]” of reconstitution because 5-azacytidine in “solution hydrolyzes at room temperature”), Table 1;
- Ex.2031(Weiss), 413-414 (reporting that 5-azacytidine needs to be “given immediately” intravenously after being dissolved in solution), 418;

- Ex.2090(Karon) (disclosing 5-azacytidine should be injected “within 15 min[utes] of reconstitution since the drug begins to decompose in aqueous solution within 1 h[ou]r”);
- Ex.2100(McCredie) (disclosing intravenous administration “immediately” after reconstitution in solution);
- Ex.2127(VoglerII) (disclosing that without using a specially formulated solution 5-azacytidine “must be given by rapid intravenous infusion because of its instability”).

35. In addition to hydrolytic degradation, 5-azacytidine is broken down by an enzyme called “cytidine deaminase,” which renders the drug ineffective. Researchers measured the rate of enzymatic deamination of 5-azacytidine and concluded that it also “may compromise the effectiveness of 5-azacytidine in treating human leukemia.” Ex.2009(Chabner), 2763, 2765.

36. By the end of the 1970s, researchers understood 5-azacytidine’s instability to limit its bioavailability and clinical use. *See, e.g.*, Ex.1014(Chan), 807 (5-Azacytidine “has long been known to be unstable in aqueous solution... attributed to [its] facile hydrolytic cleavage,” and “[c]onsequently, proper formulation has been a problem in its clinical use.”); Ex.2024(Notari), 1157 (concluding that the “apparent instability of 5-azacytidine suggests that it would be prudent to prepare solutions shortly before use to avoid significant degradation”).

37. Early attempts to develop oral formulations were unsuccessful. The difficulty in orally administering 5-azacytidine led researchers to suggest alternative strategies such as “the use of prodrugs to modify chemical and enzymatic instability, and/or the use of enzymatic inhibitors.” Ex.2041(WO2008/028193), ¶¶[0007], [0008]-[0011]. These strategies had limited success. Researchers found that administering 5-azacytidine solutions by oral intubation to mice resulted in “much lower” blood levels of the drug than when injected. Ex.2101(Neil), 463, 464. Researchers did not see any increase in hemoglobin production in baboons receiving oral 5-azacytidine concluding that “only a fraction of the administered amount [wa]s available” potentially because 5-azacytidine “is rapidly deaminated... by cytidine deaminase....” Ex.2077(DeSimone), 285, 283-284. Researchers working on sickle cell anemia saw no effect when oral 5-azacytidine was given alone, instead only seeing an increase in F reticulocyte production if given with tetrahydrouridine. Ex.1031(Dover), Abstract, 528. Additionally, even when administered to β -thalassemia patients with a cytidine deaminase inhibitor, 5-azacytidine “was ineffective.” Ex.2079(Dunbar), 467.

38. Researchers in the 1980s continued to perform experiments and recognize a “major problem encountered in the clinical formulation of 5-azacytidine is its chemical instability....” Ex.2021(Lin), 1229. By 1986, some

considered abandoning 5-azacytidine in favor of searching for alternatives chemotherapeutics. Ex.2074(Covey). A 1987 review of 5-azacytidine researchers from the NIH stated that there was no “definitive roll” for 5-azacytidine in treating leukemias due to its chemical instability in solution and enzymatic degradation. Ex.2034(Glover), 742.

39. That is, from the 1970s through the 1990s, researchers and clinicians routinely reported that 5-azacytidine was unstable. In addition to the discussion above, exemplary disclosures of 5-azacytidine’s instability from this period are provided below:

- “The instability of azacytidine in the aqueous solutions studied suggests that the drug should be administered [by injection] immediately after preparation....” Ex.2011(Cheung), 1159.
- “In aqueous solutions 5-azacytidine decomposes rapidly....” Ex.2131(Zielinski), 5029.
- 5-azacytidine’s “triazine ring is highly susceptible to reduction and nucleophilic reactions. Thus, ... 5-AC, undergoes decomposition in aqueous solution to inactive products through the addition of water to its 5-6 double bond with concomitant ring opening.” Ex.2121(Surbone), 1220.
- “[H]ydrolytic decomposition of [5-azacytidine] at neutral pH values can occur with opening of the triazine ring producing compounds of unknown biological effects.” Ex.2083(Futterman), 907.
- 5-azacytidine “is unstable in aqueous solution at neutral pH and decomposes to a compound of unknown biological activity.” Ex.2066(Antonsson), 3672.

40. The difficulties in developing a stable and biologically available formulation of 5-azacytidine persisted through the early 2000s. For example,

reflecting on over thirty years of study, researchers acknowledged that 5-azacytidine “ha[s] not been dramatically successful, and pose[s] significant restrictions on dosing schedule adjustments because of [its] instability in aqueous solution and [its] side effects.” Ex.2003(Aparicio), 632; *see also* Ex.2070(Ben-Kasus), 130 (noting 5-azacytidine’s “well-documented aqueous instability” leaves only a fraction of what is initially administered). Further, researchers in the early 2000s remained aware that, besides hydrolysis, “the ubiquitous cellular enzyme cytidine deaminase” deaminates 5-azacytidine “result[ing] in total loss of activity.” Ex.2017(Gaubert), 838.

D. Injectable 5-Azacytidine

41. By the 2000s, scientists were able to address the stability problems of 5-azacytidine by developing an injectable formulation that is administered shortly after reconstituting it. The FDA approved 5-azacytidine as an injectable suspension (Vidaza®) for subcutaneous administration in 2004. Ex.1007(Vidaza® Label 2004), 0008, 0023-0024; *see also* Ex.1008(Vidaza® Label 2007), 0008, 0011; Ex.2018(Kaminskas), 176. Vidaza® is a lyophilized formulation that requires administration shortly after reconstitution in liquid to limit degradation and achieves a therapeutic pharmacokinetic profile before metabolism, hydrolysis, and degradation eliminate the drug. Ex.1007(Vidaza® Label 2004), 0008, 0023-0024; *see also* Ex.1008(Vidaza® Label 2007), 0008, 0011.

E. Oral 5-Azacytidine

42. I understand that injecting Vidaza® causes patient discomfort because it requires injection of a large volume of liquid. Ex.2053(Blum), ¶32; Ex.1007-0018-0021(Vidaza® Label 2004); Ex.1017-0002(Marcucci). The injection also presents the risk of injection-site infections. Ex.2053(Blum), ¶32; Ex.2118(Sorrentino), 4, 20. It also burdens both patients and caregivers, who must travel to a clinic to receive daily injections of 5-azacytidine for seven consecutive days, repeated every four weeks. Ex.2053(Blum), ¶44. There was therefore still a desire to develop an orally-administered formulation to overcome those issues with the injectable formulation of 5-azacytidine. Ex.2076(Curtiss), 570, 573, 575; Ex.2053(Blum), ¶¶33, 44.

43. However, the challenges of working with 5-azacytidine that had frustrated efforts to develop an oral formulation for decades still remained. Researchers still had to contend with the “poor bioavailability” of 5-azacytidine “presumably due to the degradation of the cytidine analog by cytidine deaminases as well as [its] inherent chemical instability in the gastric environment.” Ex.1021(Sands), ¶¶[0012], [0029]-[0030]. Even after Vidaza®’s approval, 5-azacytidine’s instability continued to “limit[] [its] clinical application.” Ex.2022(Mund), 8; *see also* Ex.2018(Kaminskas), 177 (reiterating that 5-azacytidine “undergoes spontaneous hydrolysis in aqueous solutions, as well as

rapid deamination by cytidine deaminase and subsequent degradation.”);

Ex.2029(Stresemann), 8 (researchers still “widely considered [5-azacytidine] to be unstable” leading them to “handle[it] with considerable care, both in the laboratory and in the clinic.”); Ex.2010(Chen), 21 (working to find appropriate modifications to overcome 5-azacytidine’s “disadvantages in clinical application, such as difficulty to traverse biological membranes and skin layers due to poor lipophilicity, spontaneous hydrolysis in aqueous solutions and rapid deamination by cytidine deaminase, etc.”).

44. Researchers knew that acidic solutions cleaved important bonds in 5-azacytidine and this “interferes with a potential oral administration of” it.

Ex.2029(Stresemann), 8. Given the known issues, some pharmaceutical companies searched for alternatives to 5-azacytidine for oral administration. For example, some researchers attempted to develop salt analogs of nucleotides, including 5-azacytidine, “to overcome three major hurdles” including “hydrolytic degradation in aqueous environment; low solubility in most pharmaceutically acceptable solvents; and minimal oral bioavailability.” Ex.1019(Redkar), ¶[0106]. Other researchers investigated using prodrugs, precursors to pharmaceutically effective agents, to overcome 5-azacytidine’s “short half-life[] in aqueous solutions and low bioavailability....” Ex.2132(Ziemba), 2. By 2008, no therapeutically

effective oral tablet formulation for 5-azacitidine was known. Ex.2087(Grønbæk), 395.

VI. THE '628 PATENT

A. The Invention of Orally-Administered 5-Azacytidine

45. I have spoken with one of the inventors of the '628 patent, Dr. Jeff Etter and I have read his declaration (Ex.2054). I understand that before arriving at the invention of the '628 patent, Dr. Etter believed that the oral administration of 5-azacytidine would require using an enteric formulation consistent with the understanding in the field at the time that 5-azacytidine is unstable and enzymatically degraded. This is consistent with my opinion that a POSA would have used an enteric coated tablet to formulate oral 5-azacytidine, consistent with the state of the art at the time.

46. In 2006-2007, Pharmion described its preliminary efforts to develop an oral dosage form of 5-azacytidine. Ex.1034(Stoltz); Ex.2040(Ward); Ex.1010(Pharmion PR). These studies noted that “[a]zacytidine presents several significant challenges with respect to oral administration including sub-optimal physiochemical characteristics, hydrolytic instability, and active enzymatic degradation - all non-conducive to high passive intestinal tract absorption.” Ex.1034(Stoltz), 4850. Indeed, while the Pharmion studies do not disclose a formulation, Stoltz states that 5-azacytidine “*must* be formulated to avoid the

chemical and enzymatic degradation occurring presystemically.” *Id.* (emphasis added). Consistent with undergoing presystemic degradation, the preliminary studies by Pharmion showed that orally administered 5-azacytidine was 18% bioavailable as compared to subcutaneous administration. Ex.1010(Pharmion-PR).

B. Non-Enterically Coated Formulations

47. I understand that Dr. Etter’s team of inventors arrived at the current invention serendipitously. Ex.2054(Etter Decl.), ¶¶26-32. I have been informed that the inventors initially designed an enteric-coated formulation, but that the enteric coating was inadvertently “leaky.” *See* Ex.1001(’628 patent), 64:19-21. This led the inventors to consider whether 5-azacytidine could be successfully administered in a non-enteric coated formulation. After developing and testing non-enteric coated tablet formulations, the inventors made the “surprising discovery that 5-azacytidine and related compounds are best absorbed and most efficaciously delivered if instantly released, upon oral administration, in the upper gastrointestinal tract, e.g., the stomach.” Ex.1051(61/201,145), ¶[0022].

48. The invention of the ’628 patent led to the development of the first FDA-approved orally-administered formulation of 5-azacytidine, Onureg®. *See* Section XIII.E; Ex.2053(Blum Decl.), ¶15.

C. Specification

49. The '628 patent describes 5-azacytidine and its known anti-tumor activity. *See, e.g.*, Ex. 1001('628 patent), 3:28-47. The patent acknowledges that oral administration of 5-azacytidine “would be more desirable and convenient for patients and doctors” than administration by injection, but the patent also recognizes that “oral delivery of cytidine analogs has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor permeability.” Ex. 1001('628 patent), 3:48-56. The patent also explains that it was understood in the literature that oral tablet formulations of cytidine analogs, such as 5-azacytidine, “have required [an] enteric coating of the drug core” to protect against “hydrolysis in the stomach” and to ensure that the drug reaches “specific regions of the lower gastrointestinal tract” where it is “preferably absorbed....” Ex. 1001('628 patent), 3:57-4:7.

50. Against this background, the '628 patent explains the inventors' unexpected discovery that 5-azacytidine can be orally administered as a non-enterically coated tablet formulation. *See, e.g.*, Ex. 1001('628 patent), 68:50-71:44, Table 8, Table 10; *see also* Ex.1051('145 provisional), ¶[0022]. The patent's specification discloses manufacturing non-enteric coated tablets of 5-azacytidine using direct tablet compression. Ex.1001('628 patent), Tables 3-5, 7, Figure 1, 64:11-53. Consistent with limiting 5-azacytidine's exposure to water, in

Example 1, the hydroxypropyl cellulose film coating was dispersed using organic solvents. Ex. 1001('628 patent), 64:47-49. Example 2 describes additional studies that showed aqueous film coating did not have a significant effect on hydrolytic degradation of 5-azacytidine. Ex. 1001('628 patent), 67:31-38, Table 6. None of the exemplary formulations provided in Tables 3-5, 7 disclose a sugar-coated tablet formulation because there is no sugar component listed in the formulations.

Ex.1001('628 patent), Tables 3-5, 7. The formulations were then used in clinical studies and the specification reports pharmacokinetic and efficacy data following the oral administration of non-enterically coated tablets of 5-azacytidine.

Ex.1001('628 patent), 67:61-74:62, Tables 3-5, 7

D. Prosecution History

51. The Patent Office extensively and substantively examined U.S. Patent Application 12/466,213 (Ex.1022(File History)) before granting it as the '628 patent.

52. During prosecution, the Applicant overcame multiple rejections by establishing that a tablet without an enteric coating was novel and unique. *See, e.g.,* Ex.1022(File History), 0651-0653, 0714-0733, 1079-1082, 1107-1121, 2020-2024, 2063-2084. As part of the prosecution, Dr. Charles L. Beach submitted a declaration supporting the Applicant's arguments. Ex.1022, 2086(Beach Decl.); *see also id.*, 2069, 2078-2079. Dr. Beach explained that at the time of the

application, there was a strong prejudice against developing an immediate release, non-enteric coated tablet oral formulation of 5-azacytidine due to its chemical and enzymatic instability and poor permeability. Ex.1022, 2087-2089(Beach Decl.), 2073. Dr. Beach's support included data present in the application itself and post-filing data demonstrating that the claimed oral, non-enteric coated tablet formulations of 5-azacytidine result in unexpected pharmacokinetic, pharmacodynamic, and clinical properties compared to enteric coated tablet formulations. Ex.1022, 2090-2092(Beach Decl.), 2079-2084.

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

E. Claims

54. The patent includes two independent claims: claim 1 and claim 28. Independent claim 1 of the '628 patent is reproduced below:

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

55. Challenged claims 2, 6-9, and 11-27 each depend from independent claim 1. Claims 2, 6-9, 13-17, 23-27 are reproduced below:
- 2.** The composition of claim 1, wherein the at least one pharmaceutically acceptable excipient is selected from mannitol, microcrystalline cellulose, crospovidone, and magnesium stearate.
 - 6.** The composition of claim 1, which is essentially free of a cytidine deaminase inhibitor.
 - 7.** The composition of claim 1, which is essentially free of tetrahydrouridine.
 - 8.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 40 mg.
 - 9.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 400 mg.
 - 13.** The composition of claim 1, wherein the tablet further comprises a sugar coating, a film coating, or a compression coating.
 - 14.** The composition of claim 13, wherein the film coating is a cellulose ether polymer.
 - 15.** The composition of claim 14, wherein the cellulose ether polymer is hydroxypropyl methyl-cellulose, hydroxypropyl cellulose, or methyl-cellulose.
 - 16.** The composition of claim 1, wherein the amount of 5-azacytidine is 40 to 480 mg.
 - 17.** The composition of claim 1, wherein the amount of 5-azacytidine is 80 to 480 mg.
 - 23.** The composition of claim 1, wherein the amount of 5-azacytidine is 120 to 480 mg.
 - 24.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 300 mg.

- 25.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 360 mg.
- 26.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 400 mg.
- 27.** The composition of claim 1, wherein the amount of 5-azacytidine is at least about 480 mg.
- 56.** Independent claim 28 of the '628 patent is reproduced below:
- 28.** A method for treating one or more symptoms of a disease associated with abnormal cell proliferation, comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of 5-azacytidine and at least one pharmaceutically acceptable excipient, wherein the composition is a non-enteric coated tablet, and wherein the disease associated with abnormal cell proliferation is myelodysplastic syndrome or acute myelogenous leukemia.
- 57.** Challenged claims 32-36 and 38-43 each depend from independent claim 28. Claims 32-36 are reproduced below:
- 32.** The method of claim 28, wherein the method further comprises not co-administering a cytidine deaminase inhibitor with the 5-azacytidine.
- 33.** The method of claim 28, wherein the composition is a single unit dosage form.
- 34.** The method of claim 28, wherein the at least one pharmaceutically acceptable excipient is selected from mannitol, microcrystalline cellulose, crospovidone, and magnesium stearate.
- 35.** The method of claim 28, wherein the amount of 5-azacytidine is at least about 40 mg.
- 36.** The method of claim 28, wherein the amount of 5-azacytidine is at least about 400 mg.

VII. THE PETITION

58. I understand that the Petition requests cancellation of the following claims of the '628 patent: 1, 2, 6-9, 11-28, 32-36, and 38-43. *See, e.g.*, Pet., 6. All of the dependent claims depend directly or indirectly from independent claims 1 or 28. Ex.1001('628 patent), claims 2, 6-9, 11-27, 32-36, and 38-43; Pet., 18.

59. It is my understanding that the Petition requests cancellation of the claims of the '628 patent for 3 reasons:

- Ground 1: alleged anticipation of claims 1, 2, 6-8, 11, 13-18, 20-23, 28, 32-35, 38, 40, 42, and 43 based on Ionescu (Ex.1004);
- Ground 2: alleged obviousness of claims 1, 2, 6-9, 11-28, 32-36, and 38-43 over Ionescu (Ex.1004) in view of Atadja (Ex.1005), Gibson (Ex.1006), and the knowledge of a POSA; and
- Ground 3: alleged obviousness of claims 1, 2, 6-9, 11-28, 32-36, and 38-43 over Ionescu (Ex.1004) in view of Pharmion-PR (Ex.1010), Atadja (Ex.1005), Gibson (Ex.1006), and the knowledge of a POSA. *See* Pet., 1-3.

60. It is also my understanding that the dependent claims recite all of the limitations in the independent claims from which they depend, and then add additional limitations. If the Petition fails to establish that the independent claims are invalid as anticipated and obvious, then the dependent claims also cannot be anticipated or obvious.

VIII. THE ASSERTED REFERENCES

A. Ionescu (Ex.1004)

61. Ionescu is a patent reference directed to crystalline structures of 5-azacytidine and “relat[ing] to the isolation of crystalline polymorphic and pseudopolymorphic forms of 5-azacytidine....” Ex.1004(Ionescu), 1:8-10, 2:7-9.

Ionescu discloses X-ray powder diffraction patterns for “eight different polymorphic and pseudopolymorphic crystalline forms (Forms I-VIII)” of 5-azacytidine. Ex.1004(Ionescu), 2:11-14; 3:7-12:6; Figs. 1-8. Ionescu further discloses the existence of an amorphous form of 5-azacytidine and methods for synthesizing several of the disclosed forms. Ex.1004(Ionescu), 2:11-14, 2:23-26; 12:7-12:10; 15:5-22:26. Ionescu discloses that different crystal or pseudocrystal structures “may affect, for example, the solubility [and] stability” of active pharmaceutical ingredients, such as 5-azacytidine. Ex.1004(Ionescu), 1:22-25, 1:28-31.

62. Ionescu notes that 5-azacytidine may be used in treating diseases such as MDS. Ex.1004(Ionescu), 1:10-11. While Ionescu provides a generic, laundry-list disclosure of types of formulations, it does not provide specific details or examples of 5-azacytidine formulations. Ionescu provides a general disclosure of “pharmaceutical compositions comprising the various forms of 5-azacytidine together with one or more pharmaceutically acceptable excipients, diluents, or

carriers.” Ex.1004(Ionescu), 2:26-28. Ionescu discloses a generic list of many different types of pharmaceutical formulations without any preference for oral formulations of any kind. Ex.1004(Ionescu), 12:11-14:29; *see also* Ex.1004(Ionescu), 12:17-25. Separately, without further guidance and without reference to any particular embodiment or formulation, Ionescu discloses that “[t]he compositions of the invention can be formulated so as to provide quick, sustained, controlled, or delayed release of the drug substance after administration to the patient by employing procedures well known in the art.” Ex.1004(Ionescu), 13:7-10.

63. The only working example in Ionescu is an injectable slurry of 5-azacytidine. Ex.1004(Ionescu), 2:16-18, 6:15-20, 9:11-16, 21:23-22:6. Ionescu does not disclose any working examples or data of an oral formulation of 5-azacytidine, nor does it address the known chemical and enzymatic instability issues with orally administering 5-azacytidine, let alone purport to solve them.

B. Atadja (Ex.1005)

64. Atadja “relates to a combination which comprises (a) one or more chemotherapeutic agents and (b) a histone deacetylase inhibitor...especially for use in the treatment of proliferative diseases...in a mammal, particularly a human,” “pharmaceutical compositions comprising such a combination,” “a method of preventing or treating proliferative diseases...with such a combination,” and “a

commercial package or product comprising such a combination” and discloses histone deacetylase inhibitors as well as their structures. Ex.1005(Atadja), Abstract; 9:15-22:5. Atadja also discloses that the phrase ““chemotherapeutic agent(s)’ is [] broad,” and provides a long list of compounds. Ex.1005(Atadja), 2:23, 3:1-24; *see also* Ex.1005(Atadja), 3:25-9:14 (providing examples of chemotherapeutic agents). Atadja refers to 5-azacytidine as only one possible chemotherapeutic option for administration in combination with a histone deacetylase inhibitor. *See, e.g.*, Ex.1005(Atadja), 26:28-27:16.

65. For the chemotherapeutic agents, Atadja states that “[p]referably, the compounds or the pharmaceutically acceptable salts [of the chemotherapeutic agents], are administered as an oral pharmaceutical formulation in the form of a tablet, capsule or syrup; or as parenteral injections if appropriate.” Ex.1005(Atadja), 27:16-18.

66. Atadja does not disclose any working examples or data of an oral formulation of 5-azacytidine, nor does it address the known chemical and enzymatic instability issues with orally administering 5-azacytidine, let alone purport to solve them.

C. Gibson (Ex.1006)

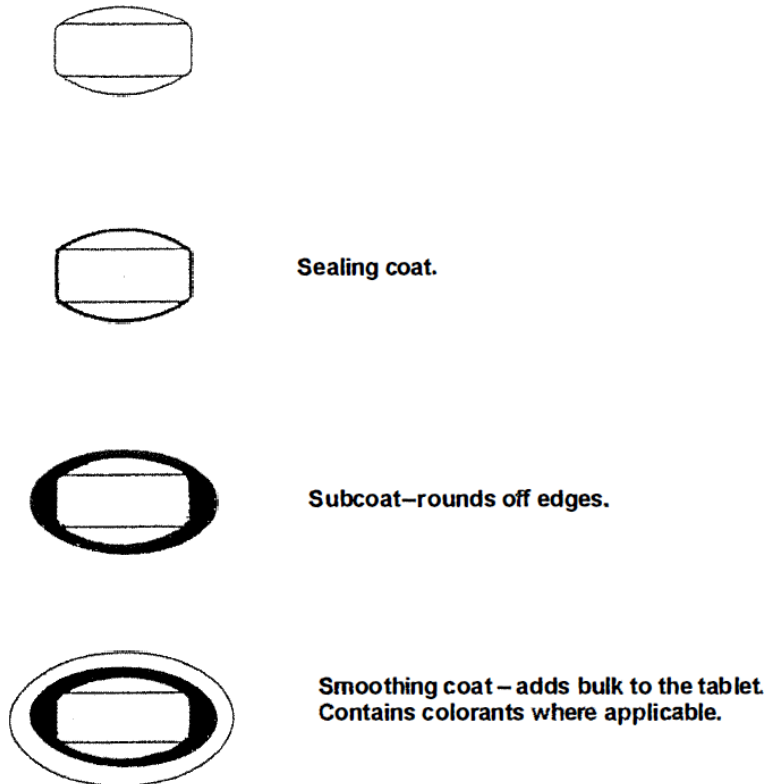
67. Gibson is a general reference textbook. It is “intended to be a practical guide to pharmaceutical preformulation and formulation” that “can be

used as a reference source and a guidance tool for those working in the pharmaceutical industry or related industries....” Ex.2063(Gibson Supplemental),

1. “Special considerations and issues for the formulation development of each route [of administration] and type of dosage form are discussed” in Gibson.

Ex.2063(Gibson Supplemental), 11. According to Gibson, oral solid dosage forms may be sugar-coated through a “multistep process” typically employing “three types of coats: a sealing coat, a subcoat and a smoothing coat.” Ex.1006-0062(Gibson); *see also* Ex.1006-0063(Gibson) (depicting the “Stages of sugar coating”). The multiple stages of sugar coating are depicted in Figure 11.24 reproduced below.

Figure 11.24 Stages of sugar coating.



Ex.1006-0063(Gibson).

68. Gibson discloses that “[o]ne of the reasons for [sugar] coating tablets is to protect the drug substances from environmental factors such as moisture” and that the sealing coat ensures that coating solutions do not penetrate into the core.

Ex.1006-0063(Gibson). Gibson discloses enteric coated tablets as well as non-enteric coated tablets. *See, e.g.*, Ex.1006-0068(Gibson). Gibson also explicitly notes that sugar-coated tablets may be enterically coated. Ex.1006-0070(Gibson) (“The original enteric coating material [shellac], originally used in sugar-coated tablets.”). In fact, Gibson discloses 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 the gastric juice.*” Ex.1006-0068(Gibson) (emphasis added).

Gibson does not mention 5-azacytidine or any treatment of MDS or AML.

D. Pharmion-PR (Ex.1010)

69. Pharmion-PR is a press release. Pharmion-PR provides high level results of a pilot study designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered 5-azacytidine in patients with MDS, AML, or solid tumors. Ex.1010-0005(Pharmion-PR).

Pharmion-PR discloses that the pilot study had concluded and that an 80mg dose given to three patients resulted in an oral bioavailability of 18% compared to subcutaneous Vidaza®. Pharmion-PR disclose that based on the results of the pilot study a subsequent multi-dose escalating study of oral 5-azacytidine was being performed. Ex.1010-0005(Pharmion-PR). Pharmion-PR does not disclose the oral formulation of 5-azacytidine employed in either study.

IX. SUMMARY OF OPINIONS

70. In my opinion, Petitioner has failed to establish claims 1, 2, 6-9, 13-17, 23-28, and 38-43 of the '628 patent are unpatentable.² It is my opinion that none of these claims is unpatentable as anticipated or obvious in view of the Grounds presented by Petitioner.

71. **First**, Ionescu does not anticipate claims 1, 2, 6-8, 13-17, 23, 28, and 32-35 (Ground 1) because (1) Ionescu does not disclose that the tablets coated with sugar are a non-enteric coated tablet as required by all of the claims and (2) Ionescu does not enable the claims. *See* Section X. Additionally, (3) Ionescu does not disclose a film coated tablet as required by claims 14 and 15. *See* Section X.B

72. **Second**, the asserted art in Ground 2 does not render obvious claims 1, 2, 6-9, 13-17, 23-28, and 32-36 because the asserted art (1) does not motivate a POSA to pursue and select an oral, non-enteric coated tablet of 5-azacytidine and (2) does not provide a reasonable expectation of success that a non-enteric coated tablet formulation would have been therapeutically effective. *See* Section XI. Additionally, the asserted art (3) does not render obvious exclusion of a cytidine deaminase inhibitor as required by claims 6, 7, and 32 (see Section XI.C), and (4)

² I understand that Dr. Grass has opined that dependent claims 11, 12, 18-22, and 38-43 are not unpatenable.

render obvious the dose values of claims 9, 24, 25, 26, 27, and 36 (see Section XI.D).

73. **Third**, the asserted art in Ground 3 does not render obvious claims 1, 2, 6-9, 13-17, 23-28, and 32-36 for the same reasons as Ground 2. *See* Section XII.

74. **Fourth**, secondary considerations (skepticism, unexpected results, industry praise, and long-felt unmet need) further demonstrate that the non-enteric coated oral tablet formulation of 5-azacytidine is inventive, non-obvious, and patentable. *See* Section XIII.

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

A. Petitioner Failed to Show that Ionescu Discloses a Non-Enteric Coated Tablet as Required by All of The Claims Challenged in Ground 1

75. Petitioner relies on a sugar-coated tablet of Ionescu as teaching the “non-enteric coated tablet” limitation. Petitioner fails to show that all limitations of independent claims 1 or 28 are disclosed in Ionescu because Petitioner fails to establish that Ionescu discloses “a non-enteric-coated tablet.” For at least this reason, Ground 1 also fails with respect to the challenged dependent claims.

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

76. Petitioner states “the sugar-coated tablets of Ionescu are NEC [non-enteric coated]....” Pet., 22. Petitioner’s analysis is incorrect and unsupported.

77. It is undisputed that a “non-enteric-coated” formulation is one “that does not comprise a coating intended to release the active ingredient(s) beyond the stomach” as described by the ’628 patent. Ex.1001(’628 patent), 11:42-45; Ex.2032(*Celgene v Accord* Claim Construction Order), 1; Pet., 20. Enteric coated tablets, on the other hand, are delayed release formulations; due to their protective coating, enteric coated tablets are not soluble in highly acidic environments, such as the stomach, but readily dissolve in the near-neutral pHs, such as those present in the intestines once the tablet has passed through the stomach. Ex.1006-0068(Gibson), -0070; Ex.1030-0049(Remington); Ex.2015(Evans), 1035. Enteric coated tablets are used “to delay the release of drugs that are inactivated by the stomach contents...or may cause nausea or bleeding by irritating the gastric mucosa....” Ex.1030-0049(Remington); *see also* Ex.1006-0068(Gibson) (disclosing that “enteric coat[s are]...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.”). Thus, independent claims 1 and 28 require a non-enteric coated tablet that does not contain a coating to prevent release of the drug in the acidic environment of the stomach. Ex.1001(’628 patent), 11:42-45.

78. Petitioner’s own cited art makes clear that sugar coatings are different coatings used for a different purpose than controlling the release of a drug. Ex.1006-0062, 72(Gibson); Ex.1030-0009(Remington). That is, a POSA would

have recognized that sugar coatings are different from and unrelated to whether the formulation has an enteric or non-enteric coating. While an enteric or non-enteric coating is used to control the release profile of a drug, sugar coatings are used to produce an “[e]legant final product,” “for identification purposes,” and to provide “protection from [the] environment” (Ex.1006-0072(Gibson)) including protection from moisture, air, and light. Ex.1006-0062(Gibson); *see also* Ex.1030-0009(Remington) (disclosing sugar coatings “may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation.”).

79. Additionally, the art as a whole makes clear that the use of a sugar coating would **only** inform a POSA that a formulation is a certain type of multilayered formulation without providing information regarding its release profile. As Petitioner’s reference, Gibson, discloses, the sugar-coating process is one of the oldest, major techniques for applying coatings to pharmaceutical dosage forms. Ex.1006-0062(Gibson). Gibson describes sugar-coating as a “multistep process” resulting in “a sugar coating...consist[ing] of three types of coat: a sealing coat, a subcoat and a smoothing coat....” Ex.1006-0062(Gibson). Petitioner also cites Remington, another standard formulation textbook that is consistent with Gibson. Remington discloses: “Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar

coating, (2) film coating, (3) microencapsulation, and (4) compression coating.”

Ex.1030-0047(Remington). Remington goes on to disclose that “sugar coating is a multistep process” that includes the steps of sealing, subcoating, and smoothing.

Ex.1030-0047(Remington). Gibson depicts this “multistep process” in Figure 11.24 reproduced below.

Figure 11.24 Stages of sugar coating.



Sealing coat.



Subcoat—rounds off edges.



**Smoothing coat – adds bulk to the tablet.
Contains colorants where applicable.**

Ex.1006-0063(Gibson). Gibson also lists sugar coating among the “main methods used to coat pharmaceutical tablets,” but does not mention the specific release profile of the active ingredient from the tablets. Ex.1006-0062(Gibson); *see also* Ex.1030-0047(Remington).

80. As such, a POSA would have understood a sugar-coated tablet does not mean that it is a non-enteric coated tablet. A POSA would need more information to make any such determination. Petitioner fails to address the disclosure of its own exhibits and throughout the literature which clearly demonstrates that Ionescu’s disclosure that a sugar coating can be applied to a tablet provides no teaching of a non-enteric coated tablet formulation of 5-azacytidine. Pet., 22-23; *see also* Ex.1006(Gibson), 0070; Ex.1030-0047, 0049-50(Remington), 0047, 0049-0050; Pet., 22; Ex.1002(Buckton Decl.), ¶83.

81. In fact, a sugar-coated tablet can include a layer of coating that is an enteric coating or non-enteric coating, which Petitioner fails to address. For example, Gibson not only discloses enteric coated and non-enteric coated tablets (*see, e.g.*, Ex.1006-0068(Gibson)), it also specifically states that sugar-coated tablets may be enterically coated (Ex.1006-0070(Gibson) (“The original enteric coating material [shellac], originally used in sugar-coated tablets.”)). Likewise, Remington discloses that the first step in the sugar-coating process is to apply a seal coat to the tablet core (Ex.1030-0047(Remington); *see also* Ex.2028(Remington 2005), 889, 930), and that “[i]f an enteric-coated [sugar-coated] product is required, additional quantities of the seal-coat solution are applied” or “synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate”—both of which are enteric coatings—are used. Ex.1030-

0047(Remington), -0049-0050; Ex.2028(Remington 2005), 889, 930. As “[e]nteric coatings [are] used for tablets containing drug substances that are inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delay[ing] release of the medication” (Ex.1030-0047(Remington); *see also* Ex.2028(Remington 2005), 890), a tablet with a sugar coating may be a delayed release tablet. Neither Petitioner nor Petitioner’s experts address this common understanding that a tablet with a sugar coating may be formulated with a coating layer that controls or delays the release of the drug, which creates a sugar-coated, enteric coated tablet.

82. It is clear from additional foundational literature in the field that a POSA would not understand a disclosure of a sugar coating without more to disclose a non-enteric coating. Lieberman, a pharmaceutical formulation textbook, states, for example, the “sugar-coating process” starts with sealing to ensure “product stability (both physical and chemical)” “and to prevent some tablet core ingredients from migrating into the coating....” Ex.2020(Lieberman), 79-80; *see also* Ex.1006-0063(Gibson) (“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.”). Petitioner has failed to establish that Ionescu’s disclosure that tablets “may be coated with a concentrated solution of sugar” (Petitioner’s “sugar-coated tablets”) discloses non-enteric coated

tablets as claimed. *See* Ex.1004-0015(Ionescu) 13:16-18; Pet., 22. Therefore, a POSA would have understood that the presence of a sugar coat provides no information as to whether the formulation is enterically coated or non-enterically coated.

83. Ionescu is entirely silent as to whether the disclosed formulations that may be coated with sugar are enteric coated, non-enteric coated, or some other formulation. Ex.1004-0015(Ionescu), 13:16-19 (“If coated tablets, capsules, or pulvules are desired, such tablets, capsules, or pulvules may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in the volatile organic solvent or mixture of solvents.”). Petitioner attempts to equate Ionescu’s disclosure that tablets may be coated with sugar with Ionescu’s separate disclosure of “quick” release (Pet., 22), but this misreads the reference. As discussed in the summary of Ionescu above, Ionescu provides generic lists of many different types of pharmaceutical formulations. *See* VIII.A. The two disclosures relied upon by Petitioner are from different paragraphs in that general disclosure, and nowhere does Ionescu say that those disclosures would be combined such that a sugar coating would result in a “quick” release or any other specific type of release. Pet., 22; Ex.1004(Ionescu), 12:7-13:21. The Petition does not acknowledge that Ionescu discusses several types of releases in the same sentence with “quick”

release, including “controlled, or delayed release[s]”. Ex.1004(Ionescu), 13:7-10 (“The 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.”). Further, Petitioner does not explain why a POSA would select quick release from the generic list of release types and specifically apply it to tablets that may be coated with sugar when Ionescu discloses several formulations, including sterile injectable solutions. Ex.1004(Ionescu), 12:22-25. Finally, as discussed above, the evidence cited in Petitioner’s own exhibits and foundational textbooks in the field clearly demonstrate that a tablet with a sugar coating, without more information, would not inform a POSA as to the nature of the tablet’s sugar coating component layers, *e.g.*, the seal coating. Ex.1006-0063-0064(Gibson); Ex.1030-0047-0048(Remington); Ex.2020(Lieberman), 79-80, 83; Ex.2028(Remington 2005), 930-931.

84. The Petition fails to establish that Ionescu anticipates the independent claims and all challenged dependent claims in Ground 1.

2. A POSA in December 2008 would at most have understood that, to the extent any 5-azacytidine tablets were coated with sugar, such tablets would be enterically coated

85. To the extent a POSA understood Ionescu to disclose an oral, coated tablet formulation of 5-azacytidine, the POSA would also have understood the

formulation to be an enterically coated tablet to avoid the stomach's acidic environment, to reduce hydrolysis, and to avoid any enzymatic degradation in the stomach before being absorbed in the intestines—not the non-enteric tablet of the claims. *See* Section XI.A-XI.B.

B. Ionescu Fails to Disclose a Film Coated Tablet as Required by Claims 14 and 15 Challenged in Ground 1

86. Nowhere does Petitioner or Dr. Buckton point to any disclosure in Ionescu of a film coating, much less the specific film coatings recited in claims 14 and 15. *See* Pet., 25-26; Ex.1002(Buckton Decl.), ¶¶94-98. And Petitioner cannot do so because Ionescu is entirely silent on film coatings. Ex.1004(Ionescu); Ex.2050(Buckton Tr.), 81:8-19.

C. Ionescu Is Not Enabling

87. I understand that to anticipate, a printed publication must also be enabling so that a POSA can practice the embodiment relied upon as anticipatory, without undue experimentation.

88. It is my opinion that Ionescu does not enable the challenged claims. I have analyzed the following factors:

- Factor 1: The level of one of ordinary skill
- Factor 2: The breadth of the claims;
- Factor 3: The nature of the invention;

- Factor 4: The quantity of experimentation needed to practice the embodiment relied upon as anticipatory based on the content of the disclosure;
- Factor 5: The amount of direction provided in the disclosure;
- Factor 6: The existence of working examples;
- Factor 7: The state of the prior art; and
- Factor 8: The level of predictability in the art.

89. **Factor 1:** The relative skill level of those in the art is discussed above and is relatively high (Factor 1). *See* Section III.

90. **Factors 2-3:** The breadth of the claims and nature of the invention are described above (Factors 2-3). *See* Section VI.

91. **Factor 4:** The quantity of experimentation needed is high, especially given the known instability of 5-azacytidine (Factor 4). *See* Section V.

92. **Factors 5-6:** Ionescu does not disclose and provides no guidance in making or using a sugar-coated, non-enteric coated tablet with a therapeutically effective amount of 5-azacytidine (Factor 5) and contains no working examples of any oral 5-azacytidine formulations, much less a non-enteric coated tablet (Factor 6). *See* Section VIII.A. Ionescu only discloses the preparation of 5-azacytidine suspended in an aqueous suspension, *i.e.*, “slurries,” for subcutaneous injection. *See* Ex.1004(Ionescu), 2:16-18, 6:15-20, 9:11-16, 21:23-22:6. Ionescu contains

only boilerplate recitations of pharmaceutical formulations, and it does not provide any guidance or working example of making or using a therapeutically effective oral non-enteric coated 5-azacytidine tablet.

93. **Factors 7-8:** As I explained above, the state of the prior art was complex, unpredictable, and counseled a POSA against non-enteric coated tablet formulations of oral 5-azacytidine (Factors 7-8). *See* Section V. Research into 5-azacytidine as a cancer therapeutic began nearly four decades before Ionescu, during which time, development of 5-azacytidine had proven to be complex and faced numerous challenges. *See, e.g.*, Ex.2041(WO2008/028193), ¶[0005], ¶[0007]. As previously discussed (*see* Section V), the state of the art established that it would be unpredictable for a non-enteric, orally administered tablet of 5-azacytidine to be therapeutically effective. In fact, the prior art explicitly suggested that any oral formulation of 5-azacytidine would require protection from the harsh, gastric environment, *i.e.*, an enteric coat. *See, e.g.*, Ex.2123(60/824,320); Ex.2041(WO2008/028193), ¶[0005], ¶[0007]. Ionescu does not address any of the known issues with the oral administration of 5-azacytidine nor identify a solution to those issues.

94. In view of the foregoing, it is my opinion that a POSA would have needed to engage in undue experimentation to arrive at a therapeutically-effective, non-enteric coated tablet of 5-azacytidine from Ionescu, which contains no more

than generic formulation disclosures, especially in view of the complex and unpredictable nature and state of the art as of December 2008. *See* Section V. Ionescu’s lack of actual examples of an oral formulation of 5-azacytidine, let alone any *in vivo* studies disclosing administration of an oral formulation of 5-azacytidine that suggest positive clinical activity, does not enable the “therapeutically effective amount” limitations. Accordingly, for these additional reasons, it is my opinion that Ionescu does not anticipate the claims challenged in Ground 1.

XI. THE ’628 PATENT CLAIMS ARE NOT OBVIOUS IN VIEW OF IONESCU IN COMBINATION WITH ATADJA AND GIBSON AND THE KNOWLEDGE OF A POSA (GROUND 2)

95. Petitioner fails to establish that Ionescu, Atadja, and Gibson and the knowledge of a POSA render obvious “a non-enteric-coated tablet” as recited in independent claims 1 and 28. For at least this reason, Ground 2 also fails with respect to the challenged dependent claims.

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

1. A POSA would not select a non-enteric coated tablet as the “default” choice for 5-azacytidine

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

96. As discussed above, the prior art taught that 5-azacytidine was unstable in acidic environments, like the stomach, and would be degraded by the

enzyme cytidine deaminase which presented major obstacles to prepare oral, unprotected (*e.g.*, non-enteric coated) formulations. *See* Section V. A POSA would have considered this knowledge and would not have selected an unprotected, oral formulation of 5-azacytidine as a “default.” Gibson makes clear that enteric coatings are used in situations where “the drug ... is unstable in gastric juice” (Ex.1006(Gibson), 0068), which is precisely what the prior art disclosed about 5-azacytidine. *See* Section V. The prior art disclosed that 5-azacytidine could be absorbed through the lower intestines. Ex.2041(WO2008/028193), ¶¶[0024]-[0025], [00120]-[00123], [00128], [00163], [00191]. The combination of the known instability and absorption in the colon would lead a POSA to pursue an enteric coating and is inconsistent with pursuing non-enteric coated tablets. Petitioner has cited no evidence of any prior art use of non-enteric coated tablets of 5-azacytidine. In fact, as noted above, I understand that consistent with the state of the art, even the inventors of the ’628 patent initially pursued an enterically-coated tablet formulation of 5-azacytidine. *See* Section VI.

97. Over four decades of prior art clearly established a POSA’s understanding that formulating unstable 5-azacytidine was challenging. Petitioner omits any acknowledgement of these challenges, which are described above and recognized by Petitioner’s experts. Ex.1002(Buckton Decl.), ¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46.

98. To the extent that Petitioner relies on Dr. Batchelor’s modelling as providing a motivation to select a non-enteric coated tablet, I have spoken with Dr. George Grass and reviewed his declaration (Ex.2052). Dr. Grass explains why Dr. Batchelor’s modeling is unreliable and confirms my opinion that a POSA would not be motivated to select a non-enteric coated tablet oral formulation of 5-azacytidine.

b. There is no prior art disclosure pursuing a non-enterically coated 5-azacytidine tablet

99. Petitioner argues that “a POSA would have understood that a NEC formulation of 5-azacytidine was orally bioavailable and well tolerated.” Pet., 37 (referencing Section IV.A.3). Petitioner cites to Pharmion-PR (Ex.1010), but Pharmion-PR does not disclose any details on the type of oral formulation used, as confirmed by Dr. Buckton. Ex.2050(Buckton Tr.), 90:10-19. Pharmion-PR cannot be relied on as disclosing a tablet, let alone a non-enteric tablet that was orally bioavailable and well tolerated. Pharmion-PR only discloses that some undescribed formulation was 18% bioavailable in humans relative to subcutaneous administration of Vidaza®. Ex.1010(Pharmion-PR).

100. If anything a POSA would infer that Pharmion-PR used an *enteric*-coated tablet in those studies. The press release from Pharmion is from June 2, 2007, and discusses a “pilot study” “designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered Azacitidine in

patients with [MDS], [AML], or other solid tumors.” Ex.1010-0005(Pharmion-PR). WO2008/028193 (“the ’193 PCT”), also from Pharmion, was filed in September 2007 and published in March 2008 and uses similar language to disclose “[a] clinical trial” to “assess[] the safety and tolerability of escalating doses, provide[] pilot information on the oral bioavailability of the study drug, and provide[] information on the single dose pharmacokinetics of the study drug after oral administration.” Ex.2041(WO2008/028193), ¶[00142]. The ’193 PCT discloses an *enteric*-coated tablet (*see* Example 3) and showed that an 80mg dose had 18% bioavailability compared to subcutaneously administered Vidaza®. *Id.*, ¶[00142], ¶¶[00157]-[00159]. Thus a POSA would have understood Pharmion-PR to report on the same study disclosed in the ’193 PCT with enterically coated tablets.

101. I understand that the Board also pointed to several references (Vorbruggen, Sands, Dover, Stoltz, and Ward) as supporting the position that Ionescu teaches a sugar coated tablet that is also a non-enteric coated tablet. Paper 7(DOI), 46-47. None of Vorbruggen, Sands, Dover, Stoltz, or Ward would have motivated a POSA to pursue a non-enteric coated tablet of 5-azacytidine, at least because none disclose a therapeutically effective, non-enteric coated tablet.

102. Sands (and Etter PCT) specifically states that an *enteric*-coated tablet formulation should be used. Ex.1021(Sands), ¶¶[0029]-[0030]. Vorbruggen is

directed to the class of azapyrimidines and does not disclose that its general disclosure of oral administration applies to 5-azacytidine. Ex.1016(Vorbruggen), Abstract, 4:53-59. Dover is a study in patients with sickle cell disease and reports that oral 5-azacytidine administered alone had no effect. Ex.1031(Dover), 528. Ward does not disclose the formulation used. Ex.2040(Ward).

103. With respect to Stoltz, any reliance on Pharmion's dog studies of oral 5-azacytidine from 2006 is also misplaced because the Pharmion authors state that the oral dosage form developed will move forward into additional clinical evaluation, which a POSA would understand to be the enteric coated studies described by Pharmion in 2007-2008. Ex.1034(Stoltz). Stoltz does not disclose that the formulation used was non-enterically coated tablets. Indeed, Stoltz states that 5-azacytidine "must be formulated to avoid the chemical and enzymatic degradation occurring presystemically" (Ex.1034(Stoltz))—which, if anything, would suggest the use of enterically-coated tablets. And any predictability of bioavailability to other species is limited because dogs do not express appreciable levels of the enzyme cytidine deaminase. Ex.2143(Hirayama), 153. Furthermore, Stoltz states that 5-azacytidine has "widely variable pharmacokinetic behavior." Ex.1034(Stoltz).

104. None of these references noted by the Board would have undermined a POSA's understanding that an enteric coating was necessary. Thus, it is my

opinion that there is no evidence that a POSA would have pursued a non-enteric coated formulation because a POSA would not have understood that such a formulation was orally bioavailable and well tolerated with any reasonable expectation of success.

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

105. Petitioner also argues that a POSA would select a non-enteric coated tablet because Ionescu and Atadja teach that 5-azacytidine could be administered as a “liquid syrup” which is incompatible with enteric coatings. Pet., 37. I understand that the Board found that those in the field were developing orally administered 5-azacytidine “both with and without enteric coatings,” which allegedly suggests Ionescu is “unconcerned with controlled or delayed release as most of these formulation types do not provide such control.” Paper 7(DOI), 45.

106. Neither Ionescu nor Atadja provides any examples of a liquid syrup formulation of 5-azacytidine, nor describes data for a liquid syrup formulations of 5-azacytidine in a therapeutically effective amount that overcame the long-understood instability of 5-azacytidine. *See* Section V.

107. In any event, bioavailability cannot be assumed for different dosage forms, even if both are oral dosage forms. Instead, a POSA understood that many factors influence the efficacy of pharmaceuticals including the chemical and physical properties of the drug and the dosage choice. *See* Ex.2067(Aulton), 2-3,

133. For instance, it was known that “[a] given drug may ... show differences in its bioavailability from one type of dosage form to another [even] when given by the same route, e.g. a tablet, a hard gelatin capsule and an aqueous suspension administered by the peroral route.” *Id.*, 133. The disclosure of a liquid syrup formulation would not have motivated a POSA to pursue a therapeutically effective amount of 5-azacytidine in a non-enterically coated tablet formulation with a reasonable expectation of success.

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

108. Neither Ionescu nor Atadja disclose any actual, working examples of oral formulations for 5-azacytidine. Ionescu is directed to novel crystalline forms of 5-azacytidine. *See* Section VIII.A. Atadja is directed to combinations of histone deacetylase inhibitors (HDAs) with any of several known chemotherapeutic agents (including 5-azacytidine). *See* Section VIII.B.

109. A POSA would have understood that neither Ionescu nor Atadja were focused on oral formulations for 5-azacytidine.³ Neither disclosure addresses the

³ In fact, even Dr. Buckton admits that Ionescu does not disclose film coating, the most common type of tablet formulation by 2008. Ex.2050(Buckton Tr.), 81:8-19.

long-standing stability concerns of 5-azacytidine, nor purports to solve these problems with novel dosage forms.

110. A POSA would not have been motivated to look to either Ionescu or Atadja to solve the decades-old problem of formulating an oral dosage form for 5-azacytidine because their disclosures as a whole are focused on topics other than dosage forms. Ionescu and Atadja provide no insight on formulating 5-azacytidine beyond the same generic teachings of any formulation textbook. Ionescu discloses dozens of different dosage forms and provide no guidance on which (if any) would be most appropriate for use with 5-azacytidine. Ex.1004(Ionescu), 12:12-14:31. Indeed, Ionescu fails to disclose the composition of its sugar-coated tablet with any specificity at all. Ex.1004(Ionescu), 13:11-21. Atadja discloses over 100 compounds and generically notes that they can be administered in four ways. Ex.1005(Atadja), 2-27. A POSA reading Atadja would understand that Atadja is saying to administer the compounds in the available ways for a particular drug, *not* that every compound could be administered in all four ways disclosed with any reasonable expectation of success.

111. The majority of the formulations in Ionescu are incompatible with what was understood about 5-azacytidine at the time. For example, Ionescu

discloses capsules.⁴ Ex.1004-0014(Ionescu). However, a POSA would have understood that capsules typically contain significant amounts of water or are formulated using high levels of water, which “makes them an unsuitable delivery form for drugs that are highly moisture sensitive.” Ex.1006-0070, -0073, -0082(Gibson). Indeed, 5-azacytidine was known to suffer from hydrolysis. *See* Section V. A POSA would have understood a capsule to be an unsuitable oral formulation for 5-azacytidine due to the risk of hydrolysis, and this disclosure would not have led a POSA to pursue non-enterically 5-azacytidine tablets. Ex.1006-0075, -0082(Gibson).

112. For similar reasons, a POSA would have avoided formulations that use high levels of water (*i.e.*, elixirs, suspensions, solutions, syrups, emulsions, pills) or are generically listed (*i.e.*, lozenges, powders, pulvules) and would not have been motivated to arrive at the non-enteric coated tablet of the claims based on Ionescu’s listing of these other formulation types. Ex.1030-0038(Remington); Ex.2146(Remington 1990) 296, 1523, 1527, 1530, 1629; Ex.2147(Remington 2005 II), 325-326, 716, 749, 754, 757, 1028; Ex.2065(Ansel), 682; Ex.2144(Lieberman Vol. 1), 438); *see also* Ex.1004-0015(Ionescu); Ex.1005-0028(Atadja). Several of

⁴ Capsules are not necessarily immediate release formulations and may include enteric coatings. Ex.1006-0075, -0082(Gibson).

Ionescu's "formulations" are routes of administration (*e.g.*, buccal and suppositories) and are not typical for chemotherapy drugs. Ex.2050(Buckton Tr.), 74:20-76:15; Ex.1004-0015(Ionescu); *see also* Ex.2145(Dean), 82-83, 152-153, 397, 538-539. These disclosures highlight that the references do not provide a POSA with information to rebut the well-known stability and formulation concerns.

113. When considering the disclosures of Ionescu and Atadja as whole, it is clear they do not motivate or disclose a therapeutically effective oral dosage form of 5-azacytidine. Any motivation to select a non-enteric tablet formulation of 5-azacytidine based on these references is hindsight driven.

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

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

- 1. Given the well-established instability of 5-azacytidine, a POSA would have had no reasonable expectation that a non-enteric coated tablet formulation would have been therapeutically effective**

115. Given the state of the art in December 2008, a POSA would not have had a reasonable expectation of success in developing a therapeutically effective, non-enteric coated oral tablet of 5-azacytidine. A POSA would have understood that the compound would likely be degraded before it could be absorbed or maintained in a sufficient amount in the plasma to provide a therapeutic benefit. *See* Section V. To the extent a POSA wanted to develop an oral formulation, the known instability of 5-azacytidine would have led a POSA to pursue enterically coated tablet formulations of 5-azacytidine to protect the drug from degradation before it could reach the site of absorption, which is exactly what the prior art taught before the invention of the '628 patent. Ex.2041(WO2008/028193), ¶[00192] (enteric “formulation is delivering 5-azacytidine to the colonic region, and that site is capable of efficiently absorbing 5-azacytidine without the degradation associated with cytidine deaminase.”). As discussed above, at first the '628 patent inventors themselves followed the conventional wisdom before serendipitously discovering that 5-azacytidine could be administered orally in a non-enterically coated tablet. *See* Section VI.

116. Petitioner's experts note that problems of chemical degradation of 5-azacytidine were known (Ex.1002(Buckton Decl.), ¶55; Ex.1003(Batchelor Decl.), ¶¶27, 34-35, 46), but provide no analysis as to why there would have been a reasonable expectation of success in arriving at the claimed non-enteric coated

tablet of 5-azacytidine in view of the known challenges of orally administering 5-azacytidine. Ionescu and the other underlying references do not disclose any working examples of a non-enterically coated tablet that provides a therapeutically effective amount of 5-azacytidine to patients, nor discuss why an oral dosage form of 5-azacytidine did not need to be protected from degradation contrary to expectations in the field.

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

117. I do not agree with Petitioner's assertion that a POSA would have had a reasonable expectation of success in view of "the knowledge in the art that 5-azacytidine was orally bioavailable and well tolerated...."

118. As explained above, neither Pharmion-PR (Ex. 1010) nor Stoltz (Ex. 1034), disclose a *non-enteric coated* tablet formulation. See Section XI.A.1.b. If anything, those references would have led a POSA to believe that an *enteric coated* tablet was required to achieve oral bioavailability, which is consistent with patent filings relating to that work made around the same time. See Section XI.A.1.b.

119. I have spoken to Dr. Grass and read his report and I agree that Petitioner puts forth no evidence or reasoning as to why a POSA would reasonably expect that an 80mg oral dose with an 18% bioavailability of relative to Vidaza®

would produce therapeutically effective pharmacokinetic properties. Pharmion-PR does not suggest that the 80mg oral dose itself was a therapeutically effective amount of 5-azacytidine. Pharmion-PR discloses that a dose escalation study would need to be done to determine whether the drug could be given at a dose that is both efficacious and non-toxic given the risk-benefit profile for the drug. Ex. 1010, Pharmion-PR; *see also* Ex.1011(Pharmion-PR II) (noting that the maximum tolerated dose, dose limiting toxicities, safety, pharmacokinetics and pharmacodynamic effects of oral 5-azacytidine were all yet to be determined).

120. To the extent that Petitioner relies on Dr. Batchelor's modelling as providing a reasonable expectation of success, I have spoken with Dr. George Grass and reviewed his report (Ex.2052). Dr. Grass explains why Dr. Batchelor's modeling is unreliable and confirms my opinion that a POSA would not have had a reasonable expectation of success in arriving at a therapeutically effective non-enteric coated tablet of 5-azacytidine.

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

121. Ionescu does not render the claims obvious to try because the tablet coated with sugar in Ionescu is not a non-enteric coated formulation, nor would it provide a reasonable expectation of success in view of the voluminous art

establishing that 5-azacytidine, if released in the stomach, would rapidly breakdown. *See* Section V.

122. Nothing in Atadja changes this analysis. A POSA would not have had a reasonable expectation of success in formulating 5-azacytidine in a non-enteric coated tablet, and nothing in Atadja’s disclosure of methods of administering HDAI-chemotherapeutic combinations changes that. As previously discussed, a POSA reading Atadja would understand it to disclose a parenteral injection of 5-azacytidine, as that was the known method of administration at the time. *See* Section XI.A.3.

123. Even if a POSA would have been motivated to make an oral tablet of 5-azacytidine, Petitioner fails to address that a POSA would have only formulated an enteric coated tablet to protect 5-azacytidine—not a non-enteric coated tablet that would deliver a “therapeutically effective amount” of the drug to a patient (claim 1), or treat MDS or AML (claim 28). *See* Section XI.B.

124. At least for these reasons, it is my opinion that Petitioner has not established claims 1 and 28 or any claims dependent therefrom are obvious over Ionescu in view of Atadja, Gibson, and the knowledge of a POSA (Ground 2).

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

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

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

Id., claim 32.

126. First, Petitioner relies on Ionescu, Atadja, Gibson and Vidaza® as not disclosing the use of cytidine deaminase inhibitors. But this is hardly surprising because none of these references disclose examples of oral administration of 5-azacytidine, they do not address the issue of whether or not to use a cytidine deaminase inhibitor.

127. Second, Petitioner relies on Kelley (Ex.1015) and Dover (Ex.1031). Petitioner’s reliance on Kelley (Ex.1015) is misplaced because it relates to cytosine arabinoside (ara-C) with THU and not 5-azacytidine or non-THU cytidine deaminase inhibitors. Ex.1015(Kelley), Abstract. Dover discloses that patients with sickle cell disease only responded to 5-azacytidine when cytidine deaminase inhibitor and 5-azacytidine were used together. Ex.1031(Dover), 528. Thus, Dover shows that cytidine deaminase inhibitors, including THU, were considered for administration with 5-azacytidine for treating sickle cell disease - consistent with the state of the art that 5-azacytidine is degraded by cytidine deaminase. *See* Section V. As of December 2008, the art describes that use of enzyme inhibitors was a strategy to improve oral bioavailability due to the significant degradation of 5-azacytidine by cytidine deaminase. Ex.2041(WO2008/028193), ¶[0007]. Dr.

Buckton admits that he was not aware of this strategy and generally was not aware of whether cytidine deaminase inhibitors other than THU were known by 2008. Ex.2050(Buckton Tr.), 99:16-22, 96:6-8. Aside from Kelley and Dover, Petitioner has not identified any motivation in view of the prior art to refrain from co-administering a 5-azacytidine inhibitor, including THU, with 5-azacytidine. In fact, a POSA would have no reasonable expectation of success in orally administering 5-azacytidine without a cytidine deaminase inhibitor, especially if using a non-enteric coated tablet formulation of 5-azacytidine, which as I previously discussed would not be an expected approach, because a POSA would expect the drug to be degraded. *See e.g.*, Ex.2017(Gaubert), 837-838 (deamination of 5-azacytidine by “the ubiquitous cellular enzyme cytidine deaminase (CDA)” “results in total loss of activity.”).

128. At least for these additional reasons, it is my opinion that Petitioner has not established claims 6, 7, or 32 would have been obvious over Ionescu in view of Atadja, Gibson, and the knowledge of a POSA.

D. Ionescu, Atadja, Gibson, and Knowledge of a POSA Do Not Render Obvious the Dose Values Recited by Claims 9, 24, 25, 26, 27, and 36

129. Claim 24 depends from claim 1 and recites that “the amount of 5-azacytidine is at least about 300 mg.” Ex.1001(’628 patent), claim 24. The other claims recite doses of at least about 360mg, 400mg, and 480mg. The independent

claims and thus also these dependent claims, requires the non-enteric coated, oral tablet “compris[e] a therapeutically effective amount of 5-azacytidine.”

Ex.1001('628 patent), claim 1. However, none of the art cited by Petitioner teaches a therapeutically effective amount of 5-azacytidine for a non-enteric coated tablet or that the therapeutically effective amount is at least about 300mg (or 360mg, 400mg, 480mg). Instead, Petitioner argues it would have been obvious to optimize the dosage amounts of the non-enteric coated tablets of Ionescu based on Atadja.

130. In keeping with Ionescu having only a subcutaneous example, it discloses a maximum 5-azacytidine dose of 200mg, which is close to the approved maximum dose for Vidaza®. Ex.1007-0022(Vidaza® Label 2004) (disclosing maximum dose of 100mg/m²); Ex.1017-0004(Marcucci) (disclosing average body surface area of 1.9m²). Ionescu does not disclose an oral formulation comprising 300mg of 5-azacytidine, and Atadja specifically skips certain dosages, including 300mg. Ex. 1004(Ionescu), 14:22-25; Ex.1005(Atadja), 27:13-16.

131. Atadja does not provide any support that its broad range of 200-1000mg would be therapeutically effective for 5-azacytidine administered as a non-enteric coated tablet, and it provides no reason to select the claimed dosage from the range, especially when certain doses, including 300mg, are not recited. As explained above, a POSA would not understand Atadja to be directed to non-

enteric coated tablets of 5-azacytdine (*see* Section XI.A.3) and so a POSA would not look to the reference as describing doses that are therapeutically effective in the context of a non-enteric, oral tablet formulation.

132. I understand that Petitioner argues that a POSA would have increased the dose from 200mg towards bioequivalence with subcutaneous Vidaza® and relies on Pharmion-PR to argue that there was reasonable expectation of success because the safety and oral bioavailability has already been established. As explained above, Pharmion-PR does not disclose that a non-enteric coated tablet formulation is safe and effective and only reports on administering 80mg orally using an undefined formulation (which would have been understood to be enteric coated). *See* Section XI.A.1.b. Petitioner does not identify any evidence that a 300mg dose, or any higher doses of 5-azacytidine subject to high levels of hydrolysis and degradation would achieve pharmacokinetic properties that were therapeutically effective and safe. And Petitioner points to no evidence that a POSA would select 300mg, or any higher dose, with any reasonable expectation of success without the benefit of hindsight.

133. It is my opinion that Petitioner has not established that a POSA would have a reasonable expectation of success that the claimed dosages of a non-enteric coated tablet formulation would be therapeutically effective.

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

134. Ground 2 differs from Ground 3 by the inclusion of Pharmion-PR in the grounds. But in Ground 3, Petitioner does not rely on Pharmion-PR as disclosing a claim limitation. Instead, Petitioner relies on Pharmion-PR as allegedly providing motivation to select a dosage form and amounts from Ionescu. Pet., 59-61. However, as discussed above, Pharmion-PR's disclosure that an unspecified oral formulation of 80mg was 18% bioavailable as compared to a subcutaneous dose provides no such motivation or reasonable expectation of success. *See* Sections XI.A.1.b, XI.B.2. The lack of reasonable expectation of success is supported by Pharmion-PR II, which notes that the maximum tolerated dose, dose limiting toxicities, safety, pharmacokinetics and pharmacodynamic effects of oral 5-azacytidine were all yet to be determined. Ex.1011(Pharmion-PR II). Thus, in my opinion Petitioner fails to establish that Ionescu, Pharmion-PR, Atadja, and Gibson and the knowledge of a POSA render obvious independent claims 1 and 28 and the challenged dependent claims.

XIII. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS OF THE CLAIMS

135. I have been informed that the obviousness analysis requires consideration of (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention(s), (3) the level of a POSA, and (4)

objective indicia of non-obviousness. I understand that objective indicia include concepts such as copying, long-felt but unmet need, the failure of others, commercial success, unexpected results, and skepticism; requires a nexus or link to the claimed invention; and must be considered before determining obviousness. I have addressed the first 3 factors above, and I address objective indicia of non-obviousness below.

136. In my opinion, the following objective indicia - skepticism of others, unexpected results, long-felt, unmet need, and industry praise – further demonstrate the non-obviousness of the independent claims 1 and 28. These objective indicia equally apply to claims depending from claim 1 (including claims 2, 6-8, 11, 13-18, 20-24), or depending from claim 28 (including claims 32-35, 38, 40, 42, and 43).

A. The Field Was Skeptical of A Non-Enteric Coated, Oral 5-Azacytidine Tablet

137. Before the invention disclosed in the '628 patent claims, there was significant skepticism as to whether an oral formulation of 5-azacytidine could be developed at all. And if an oral formulation could be developed, there was a belief it had to be enterically coated. For example, in 1979 it was acknowledged that, because of 5-azacytidine's long-known instability in aqueous solutions, "proper formulation ha[d] been a problem in its clinical use." Ex.1014(Chan), 807. More recently, researchers in 2006 noted that "hurdles" facing 5-azacytidine included

“hydrolytic degradation in aqueous environment... and minimal oral bioavailability.” Ex.1019(Redkar), ¶[0106]. Researchers were also skeptical due to a second “drawback”: deamination by “the ubiquitous cellular enzyme cytidine deaminase (CDA) since deamination of [5-azacytidine] results in total loss of activity.” Ex.2017(Gaubert), 837-838; *see also* Ex.2041(WO2008/028193) (“In the case of 5-azacytidine... an enzyme thought to be responsible for a significant portion of drug metabolism is cytidine deaminase.”); *see also* Section IV.

138. Researchers expressed similar concerns in peer-reviewed literature *even after the approval of Vidaza®* in 2004. *See* Ex.1034(Stoltz) (“Azacitidine presents several significant challenges with respect to oral administration including sub-optimal physiochemical characteristics, hydrolytic instability, and active enzymatic degradation - all non-conducive to high passive intestinal tract absorption.”); *see also*, Ex.2018(Kaminskas); Ex.2070(Ben-Kasus); Ex.2022(Mund); Ex.2029(Stresemann); Ex.2010(Chen); Ex.2132(Ziemba); *see also* Section V.

139. Given the extensively documented instability issues due to hydrolysis and enzymatic degradation (*see* Section V) that persisted even after the approval of Vidaza®, to the extent that the field considered oral azacytidine it focused on *enteric* coated formulations that would protect the drug from the acid environs of the stomach. *See* Section VI. To avoid the understood challenges, “attempts to

develop oral dosage forms of cytidine analogs [such as 5-azacytidine...] 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....” Ex.1001(’628 patent), 3:58-63. Further, an enteric coating would ensure release of the drug after the stomach for absorption in the colon, thereby bypassing enzymatic degradation in the stomach and upper gastrointestinal segments to reduce this additional degradation risk. *See, e.g.*, Ex.2041(WO2008/028193), ¶¶[00130], [00142], [00163].

140. Thus, the development of an oral, non-enteric coated 5-azacytidine formulation faced significant skepticism in the field at the time of the ’628 patent’s filing.

B. Unexpected Results

141. Because of the well-established belief that 5-azacytidine was chemically and enzymatically unstable and poorly permeable (*see, e.g.*, Ex.2041(WO2008/028193), ¶[0007]), there was a prejudice in the art against developing a non-enteric coated oral tablet formulation of 5-azacytidine. *See* Sections V-VI; Ex.2054(Etter Decl.), ¶¶9, 19-21; *see also* Ex.1001(’628 patent), 3:58-65; Ex.1021(Sands), ¶¶[0029]-[0030] (specifically stating that an *enteric*-coated tablet formulation should be used). Alternatively, researchers developed entirely different approaches. *See, e.g.*, Ex.2132(Ziemba), 2 (disclosing the

development of prodrug precursors to overcome 5-azacytidine's "short half-life in aqueous solutions and low bioavailability"). This prejudice was backed-up by over forty years of research and publications, so it was completely unexpected that a non-enteric tablet of 5-azacytidine exhibited its impressive pharmacokinetic, pharmacodynamic, and clinical properties.

142. For example, compared to enterically coated tablets, non-enteric coated tablets of 5-azacytidine resulted in significant delivery of the drug to recipients. *See* Ex.1001('628 patent), Figures 8-10, 12, 13, 14; 8:63-9:5; 71:56-72:17 (Table 11); 72:39-67. This outcome would have been surprising given the non-enteric coated tablets' exposure to the harsh gastric environment. Indeed, even preliminary results demonstrated the 5-azacytidine exposure achieved through administration of the non-enteric coated tablets of the invention was "comparable or better than the exposure observed" following administration of a formulation described as having a "leaky" enteric coating. Ex.1051-0018(145 provisional). As credited by the Patent Office, "[T]hese results are significant and surprising, particularly given the conventional wisdom at the time ... that 5-azacytidine would decompose in the acidic environment...." Ex.1022-2091, -2138-2139.

143. The lower drug exposure provided by non-enterically coated oral 5-azacytidine also provided surprisingly effective clinical results compared to

traditional intravenous administration. For example, researchers comparing the two administration routes found that even though oral administration only achieved a relative bioavailability of 20%, the “[k]inetics of the change in DNA methylation levels after [subcutaneous] and oral azacitidine were similar....” Ex.2084(Garcia-Manero), 440. That is, non-enterically coated oral 5-azacytidine achieves similar methylation results associated with positive clinical outcomes despite a lower bioavailability than injected doses. Such a significant result is surprising and unexpected. Thus, even starting with injectable 5-azacytidine, researchers and clinicians could not have expected to arrive at the therapeutic efficacy of the independent claims.

144. Furthermore, I understand from Dr. Etter that even the inventors were surprised by the results achieved using a non-enteric coated tablet of 5-azacytidine. Ex.2054(Etter Decl.), ¶¶21, 31, 33-35. Thus, even those working closely with 5-azacytidine did not expect the results reported in the ’628 patent, which reinforces my opinion that the results were unexpected.

C. Long-Felt, Unmet Need

145. I understand that Dr. Blum has opined on the long-felt but unmet need for a therapeutically effective oral formulation of 5-azacytidine, and the long-felt but unmet need for continued therapy for AML.

D. The Medical Industry Praised Onureg®

146. I understand that Dr. Blum has opined on praise the medical industry conferred on non-enteric coated tablets of 5-azacytidine, approved as Onureg®.

E. Nexus

147. I have been informed that nexus between the objective indicia of non-obviousness and the claims is presumed when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features and is coextensive with them. This does not require a perfect correspondence between products and claims, but a demonstration that the product is essentially the claimed invention.

148. In 2020, the FDA approved Onureg®, a non-enteric coated tablet comprising a therapeutically effective amount of 5-azacytidine, as the first oral formulation of 5-azacytidine and as the first maintenance therapy of AML patients. Ex.2062(Onureg® Label); Ex.2095(Liu).

149. As depicted in the below chart, Onureg® embodies at least claims 1, 2, 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 28, 32, 33, 34, 35, 38, 40, 42, and 43 of the '628 patent. These include claims specifically reciting dosages or pharmacokinetic values. It is my opinion that there is a link between Onureg® and the below claims. That is, the claimed invention is coextensive with Onureg®.

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
1[a].	A pharmaceutical composition for oral administration comprising	“Administer ONUREG 300 mg orally once daily on Days 1 through 14 of each 28-day cycle (2.2).” Ex.2062(Onureg® Label), 1.
1[b].	a therapeutically effective amount of 5-azacytidine and	“ONUREG is a nucleoside metabolic inhibitor indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy (1).” Ex.2062 (Onureg® Label), 1; <i>see also id.</i> (“Dosage Forms and Strengths”), 15-18 (“Clinical Studies”).
1[c].	at least one pharmaceutically acceptable excipient,	“What are the ingredients in ONUREG? Active ingredient: azacitidine Inactive ingredients: Each core tablet contains: croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose. The pink 200 mg tablet coating contains: hypromellose, iron oxide red, lactose monohydrate, polyethylene glycol, titanium dioxide, and triacetin.

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
		The brown 300 mg tablet coating contains: black iron oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, polyethylene glycol, titanium dioxide, and triacetin.” Ex.2062(Onureg® Label), 22.
1[d].	wherein the composition is a non-enteric coated tablet.	See claim 1[c] (disclosing coatings not containing enteric components (e.g., Eudragit)).
2.	The composition of claim 1, wherein the at least one pharmaceutically acceptable excipient is selected from mannitol, microcrystalline cellulose, crospovidone, and magnesium stearate.	See claim 1[c] (disclosing “core tablet[s] contain[ing] ... magnesium stearate, mannitol, and silicified microcrystalline cellulose”).
6.	The composition of claim 1, which is essentially free of a cytidine deaminase inhibitor.	See claim 1[c] (disclosing no cytidine deaminase inhibitor ingredients).
7.	The composition of claim 1, which is essentially free of tetrahydrouridine.	See claim 6.
8.	The composition of claim 1, wherein the amount of 5-azacytidine is at least about 40 mg.	“DOSAGE FORMS AND STRENGTHS Tablets: 200 mg and 300 mg (3).” Ex.2062 (Onureg® Label), 1.
11.	The composition of claim 1, which has been shown to achieve an area-under-the-curve value of at least about 200 ng-hr/mL following oral administration to a test subject.	“12.3 Pharmacokinetics The systemic exposure of azacitidine is approximately dose proportional over the dose range of 120 mg to 600 mg once daily of ONUREG (0.4 to 2 times the recommended dosage). Following a single 300 mg dose of ONUREG, the mean (coefficient

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
		of variation [CV%]) Cmax of azacitidine was 145 ng/mL (64%) and the mean AUC of azacitidine was 242 ng h/mL (65%). No accumulation was observed following ONUREG 300 mg once daily.” Ex.2062(Onureg® Label), 13.
13.	The composition of claim 1, wherein the tablet further comprises a sugar coating, a film coating, or a compression coating.	“How Supplied ONUREG tablets are available as: 200 mg: pink, oval, film-coated tablets with debossed ‘200’ on one side and ‘ONU’ on the other side. 300 mg: brown, oval, film-coated tablets with debossed ‘300’ on one side and ‘ONU’ on the other side.” Ex.2062(Onureg® Label), 18.
14.	The composition of claim 13, wherein the film coating is a cellulose ether polymer.	<i>See</i> claim 1[c] (disclosing coatings containing hypromellose).
15.	The composition of claim 14, wherein the cellulose ether polymer is hydroxypropyl methyl-cellulose, hydroxypropyl cellulose, or methyl-cellulose.	<i>See</i> claim 14.
16.	The composition of claim 1, wherein the amount of 5-azacytidine is 40 to 480 mg.	<i>See</i> claim 8.
17.	The composition of claim 1, wherein the amount of 5-azacytidine is 80 to 480 mg.	<i>See</i> claim 8.
18.	The composition of claim 1, which has been shown to achieve a maximum plasma concentration of at least about 100 ng/mL	<i>See</i> claim 11.

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
	following oral administration to a test subject.	
20.	The composition of claim 1, which has been shown to achieve a time to maximum plasma concentration of less than about 180 minutes following oral administration to a test subject.	“Absorption The mean oral bioavailability is approximately 11% relative to subcutaneous administration. The median time to peak plasma concentration of azacitidine is 1 hour.” Ex.2062-0013(Onureg® Label).
21.	The composition of claim 1, which has been shown to achieve a time to maximum plasma concentration of less than about 90 minutes following oral administration to a test subject.	See claim 20.
22.	The composition of claim 1, which has been shown to achieve a time to maximum plasma concentration of less than about 60 minutes following oral administration to a test subject.	See claim 20.
23.	The composition of claim 1, wherein the amount of 5-azacytidine is 120 to 480 mg.	See claim 8.
24.	The composition of claim 1, wherein the amount of 5-azacytidine is at least about 300 mg.	See claim 8.
28[a].	A method for treating one or more symptoms of a disease associated with abnormal cell proliferation, comprising	See claim 1[b] (disclosing continued treatment of adult patients with acute myeloid leukemia).
28[b].	orally administering to a subject in need thereof a pharmaceutical composition	See claim 1[a].

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
28[c].	comprising a therapeutically effective amount of 5-azacytidine and	<i>See</i> claim 1[b].
28[d].	at least one pharmaceutically acceptable excipient,	<i>See</i> claim 1[c].
28[e].	wherein the composition is a non-enteric coated tablet, and	<i>See</i> claim 1[d].
28[f].	wherein the disease associated with abnormal cell proliferation is myelodysplastic syndrome or acute myelogenous leukemia.	<i>See</i> claim 28[a].
32.	The method of claim 28, wherein the method further comprises not co-administering a cytidine deaminase inhibitor with the 5-azacytidine.	<i>See</i> claim 6.
33.	The method of claim 28, wherein the composition is a single unit dosage form.	<i>See</i> claim 1[a] (disclosing administering 300mg once daily); 13 (disclosing 300mg tablets).
34.	The method of claim 28, wherein the at least one pharmaceutically acceptable excipient is selected from mannitol, microcrystalline cellulose, crospovidone, and magnesium stearate.	<i>See</i> claim 2.
35.	The method of claim 28, wherein the amount of 5-azacytidine is at least about 40 mg.	<i>See</i> claim 8.
38.	The method of claim 28, which has been shown to achieve an area-under-the-curve value of at least about 200 ng-hr/mL following oral administration to a test subject.	<i>See</i> claim 11.
40.	The method of claim 28, which has been shown to achieve a maximum plasma concentration	<i>See</i> claim 18.

Claim Element	Claim Language	Exemplary Evidence of Embodiment by Onureg®
	of at least about 100 ng/mL following oral administration to a test subject.	
42.	The method of claim 28, which has been shown to achieve a time to maximum plasma concentration of less than about 180 minutes following oral administration to a test subject.	<i>See claim 20.</i>
43.	The method of claim 28, which has been shown to achieve a time to maximum plasma concentration of less than about 90 minutes following oral administration to a test subject.	<i>See claim 20.</i>

XIV. AVAILABILITY FOR CROSS-EXAMINATION

150. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

XV. RIGHT TO SUPPLEMENT

151. I reserve the right to supplement my opinions in the future to respond to any arguments that Petitioner raises and to take into account new information as it becomes available to me.

XVI. JURAT

152. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Signed: 
Dr. Cory J. Berkland

Date: 10/12/2023

APPENDIX A

Cory J Berkland

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Education and Professional Training

Sabbatical, Sofinnova Ventures, Menlo Park, CA 2014

Ph.D. Chemical and Biomolecular Engineering, University of Illinois, Urbana, IL
May 2003

M.S. Chemical Engineering, University of Illinois, Urbana, IL
May 2001

B.S. Chemical Engineering, Iowa State University, Ames, IA
December 1998

Professional Experience

Co-founder and President, Axioforce, Saint Louis, MO

2022-present Co-founder and Chief Executive Officer, Kinimmune,
Saint Louis, MO 2020-present

Co-founder, Chairman, and Chief Executive Officer, Bond Biosciences, New
York, NY 2020-present

Co-founder and Chief Scientific Officer, Bond Biosciences, New York City, NY
2015-2020

Co-founder and Chairman of the Board, Orion BioScience, Omaha, NE
2013-present

Co-founder and Chief Technology Officer, Savara Pharmaceuticals, Austin, TX
2008-2014

Co-founder and Chief Scientific Officer, Orbis Biosciences, Lenexa, KS
2007-2020

Awards

Bellows Scholar, The University of Kansas, Lawrence, KS
2018

National Academy of Inventors, Washington DC
2017

Bellows Scholar, The University of Kansas, Lawrence, KS
2016

Fellow of the American Institute of Medical and Biological Engineering
2015

Bellows Scholar, The University of Kansas, Lawrence, KS
2014

Jim Baxendale Commercialization Award, The University of Kansas, Lawrence,
KS 2014

Iowa State University Professional Progress in Engineering Award, Ames, IA
2013

Leading Light Award, The University of Kansas, Lawrence, KS
2013

Miller Scholar, The University of Kansas, Lawrence, KS
2013

Controlled Release Society Young Investigator Award, Quebec City, Canada
2012

Coulter Foundation Fellow, The Coulter Foundation
2012

University Scholarly Achievement Award, The University of Kansas, Lawrence,
KS 2012

Nagai Foundation Distinguished Lectureship, Annual DDS Conference, Shizuoka,
Japan 2011

Miller Scholar, The University of Kansas, Lawrence, KS
2011

Kemper Fellowship for Teaching Excellence, The University of Kansas, Lawrence,
KS 2010

Featured in Science Magazine Online, “The Entrepreneurial Bug”
2009

Bellows Scholar, The University of Kansas, Lawrence, KS
2008

Coulter Translational Research Award, The Coulter Foundation
2008

Teaching Achievement Recognition, Center for Teaching Excellence, Lawrence,
KS 2007

Outstanding Reviewer for the Journal of Pharmaceutical Sciences
2007

Miller Scholar, The University of Kansas, Lawrence, KS
2006

Outstanding Reviewer for the Journal of Pharmaceutical Sciences
2005

Genencor Outstanding Paper Award, Controlled Release Society, Honolulu, HI
2004

Best Presentation, Chemical and Biomolecular Engineering Symposium, Urbana, IL
2003

Graduate College Travel Award, Urbana, IL
2003

Highlights of Student Posters Award, Controlled Release Society, Seoul, Korea
2002

Whitaker Award, American Chemical Society, Particles meeting, Orlando, FL
2002

Featured Technology, University of Illinois Technology Showcase, Urbana, IL
2001

Publications

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Non-Refereed Publications

207. G. Smaldone, I. Gonda, J. Mitchell, O. Usmani, C. Berkland, and A. Clark (2013) Ask the experts: The benefits and challenges of pulmonary drug delivery, *Therapeutic Delivery* 4(8):1-9
208. C. Berkland (2011) Engineering particles and colloids for pharmaceutical and biomaterial applications, *Progress in Drug Delivery Systems XX*, Shizuoka, Japan, 1-4
209. C. Berkland (2010) “Next Steps for Pharmaceutical Nanotechnology” *Journal of Pharmaceutical Innovation* 5(3):70-71
210. C. Berkland, G. Laurence, S. Lerner, P. Soni and M. Crowley (2010) “An overview of NanoCluster powder formulation technology” *Pharmaceutical Technology* 34(10):72-74,76,78
211. M. Bailey and C. Berkland (2010) “Research Spotlight: Therapeutic Particles and Biomaterials Technology Laboratory at The University of Kansas” *Therapeutic Delivery* 1(1):29-35
212. D.W. Pack, C. Berkland, N. Varde and K. Kim (2002) Precision polymer microshells for controlled-release drug delivery, 223rd ACS National Meeting extended abstract
213. C. Berkland, K. Kim and D. Pack (2000) Fabrication of PLGA microspheres with precisely controlled, homogeneous size distribution, *Proceedings of the International Symposium on Controlled Release of Bioactive Materials*, 1130-1131

Book Chapters

1. N. El-Gendy, M. Bailey and C. Berkland (2014) “Particle Engineering Technologies for Pulmonary Drug Delivery” *Controlled Release Science and Technology: Pulmonary Delivery*, Ed. Hugh Smyth and Anthony Hickey, 283-312
2. N.H. Dormer, C.J. Berkland and M. Singh (2014) “Monodispersed Microencapsulation Technology” *Microencapsulation in the Food Industry*, Ed. N. Vasisht, A.R. Khare and R. Sobel

3. M. Bailey and C. Berkland (2010) “Modified release delivery systems” Biodrug Delivery Systems, Vol. 194, Ed. Mariko Morishita and Kinam Park, 234-247

Invited Presentations

1. C. Berkland “Delivering drugs to target compartments to treat autoimmune disease, cancer, and others”, The University of Utah, Salt Lake City, UT, April 4, 2022
2. C. Berkland “Designing immunotherapies for injection site retention or drainage to lymphatics”, 2021 CSPS/PSJ/CC-CRS Symposium, Ottawa, Canada, May 31, 2021
3. C. Berkland “A few early lessons in entrepreneurship”, University of Houston, Houston, TX, March 3, 2021
4. C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, Colorado State University, Fort Collins, CO, February 2, 2021
5. C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, University of Houston, Houston, TX, January 29, 2021
6. C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, Washington University, St. Louis, MO, March 17, 2020
7. C. Berkland “A Discussion of Venture Capital and the Role of Scientists and Physicians”, Research and Discovery Grand Rounds, The University of Kansas Medical Center, Kansas City, MO, July 20, 2020
8. C. Berkland “A Review of Clinically Tested ASIT Delivery Systems & Implications for Future Design, Antigen-Specific Immune Tolerance Drug Development, Boston, MA, February 26, 2020
9. C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, Eli Lilly, Indianapolis, IN, February 20, 2020
10. C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, Purdue University, February 19, 2020

- 11.C. Berkland “Developing a Stakeholder / Investor Pitch”, Biotech Startup School, The University of Kansas, Lawrence, KS, February 4, 2020
- 12.C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, Bristol Myers Squibb, East Brunswick, NJ, December 9, 2019
- 13.J. Whitlow, J. Salash, S. Huayamares, S. Crawl, B. Stottlemire, P. Dhar, M. He, C. Berkland “Remote control, remote sensing of soft materials”, Honeywell Advanced Materials Consortia, Knoxville, TN, June 20, 2019
- 14.J. Whitlow, J. Salash, S. Huayamares, S. Crawl, B. Stottlemire, P. Dhar, M. He, C. Berkland “Remote control, remote sensing of soft materials”, The University of Kansas, Lawrence, KS, January 24, 2019
- 15.C. Berkland “Venture capital and financing mechanisms fostering innovative start-up companies”, Self Graduate Fellowship, The University of Kansas, Lawrence, KS, January 24, 2019
- 16.C. Berkland “Competitive Leverage”, Biotech Startup School, The University of Kansas, Lawrence, KS, January 7, 2019
- 17.C. Berkland “Mimicking Properties of Natural Biomaterials as a Stem Cell Niche”, Midwest Conference on Cell Therapy and Regenerative Medicine, Overland Park, KS, September 14, 2018
- 18.C. Berkland “Manufacturing Controlled Release Powders for Patient-Friendly Dosage Forms”, Industrial Partners for Research in Interfacial and Materials Engineering, Minneapolis, MN, May 30, 2018
- 19.C. Berkland “Translating Research through New Venture Creation”, The University of Kansas, Kansas City, KS, April 19, 2018
- 20.C. Berkland “Aerosolized ceftazidime for the prophylaxis and treatment of melioidosis”, MRIGlobal, Kansas City, MO, November 8, 2017
- 21.C. Berkland “Drugs should be designed with delivery in mind (and vice versa)”, California Institute for Biomedical Research, La Jolla, CA, November 17, 2017

- 22.C. Berkland “Non-viral gene delivery to mucosal surfaces”, American Association of Pharmaceutical Scientists Annual Meeting, San Diego, CA, November 15, 2017
- 23.C. Berkland “A few early lessons in entrepreneurship”, School of Biomedical Engineering, The University of Oklahoma, Norman, OK, September 1, 2017
- 24.C. Berkland “A few early lessons in entrepreneurship”, Inaugural Distinguished Professor Lecture, The University of Kansas, Lawrence, KS, April 6, 2017
- 25.C. Berkland “Soluble antigen arrays as antigen-specific autoimmune therapy” Globalization of Pharmaceuticals Education Network, Lawrence, Kansas, November 12, 2016
- 26.C. Berkland “Entrepreneurship: Intellectual Property Strategy” Globalization of Pharmaceuticals Education Network, Lawrence, Kansas, November 12, 2016
- 27.C. Berkland “A few early lessons in entrepreneurship”, Chemical and Biomolecular Engineering Department, The University of Illinois, Urbana-Champaign, IL, October 23, 2016
- 28.C. Berkland “A discussion of venture capital and the role of scientists”, The University of Texas, Austin, TX, September 29, 2016
- 29.C. Berkland “Biomaterials and Controlled Release in Bone Tissue Engineering”, The University of Kansas Medical Center, Kansas City, KS, June 15, 2016
- 30.C. Berkland “Early Lessons in Entrepreneurship: A Venture Capital Perspective”, American Thoracic Society, San Francisco, CA, September 15, 2016
- 31.C. Berkland “Drug delivery systems for improving ocular therapeutics”, Allergan, Irvine, CA, June 2, 2016
- 32.C. Berkland “Barriers to effective gene delivery”, Cystic Fibrosis Foundation Pushing the Frontiers workshop, Chantilly, VA, June 3, 2015

- 33.C. Berkland “Polyelectrolyte complexes for gene delivery to lungs”, Cystic Fibrosis Foundation Therapeutics Gene Repair and Delivery workshop, Cystic Fibrosis Foundation, Bethesda, MD, December 3, 2014
- 34.C. Berkland “A few early lessons in entrepreneurship”, Bioengineering Department, The University of California, Berkeley, CA, October 15, 2014
- 35.C. Berkland “Controlled release delivery of proteins” Genentech, South San Francisco, California, December 21, 2014
- 36.C. Berkland “A few early lessons in entrepreneurship”, Chemistry Department, The University of Kansas, Lawrence, KS, February 19, 2014
- 37.C. Berkland “Translatable Pharmaceutical Formulations of Aerosolized and Topical Antibiotics”, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, February 18, 2014
- 38.C. Berkland “A few early lessons in entrepreneurship”, Chemical and Biomolecular Engineering Department 100 year Anniversary Symposium, Iowa State University, Ames, IA, September 27, 2013
- 39.J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland “Single-Step Grafting of Aminooxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis”, ACS annual meeting, Indianapolis, Indiana, September 9, 2013
- 40.C. Berkland “Precision Particle Fabrication”, ACS annual meeting, Indianapolis, Indiana, September 9, 2013
- 41.C. Berkland “Designing formulation and delivery with drug properties in mind”, Gordon Conference: Preclinical Form and Formulation for Drug Discovery, Waterville Valley, New Hampshire, June 5, 2013
- 42.C. Berkland “Colloids and polymers for chemical delivery”, Iowa State University, Ames, IA, April 19, 2013
- 43.S.C. Dennis, Q. Wang, S. Kieweg, M.S. Detamore and C.J. Berkland “Colloidal Gels as a New Class of ‘Bingham Plastic’ Biomaterials for Tissue

Regeneration”, CMBE annual meeting, Kohala Coast, Hawaii, January 6, 2013

44.C. Berkland “Colloids and polymers for drug and chemical delivery”, Kansas State University, Manhattan, Kansas, November 5, 2012

45.C. Berkland “Uniform PLGA Microspheres Sustain NSAID Blood Levels With Zero-Order Kinetics”, Controlled Release Society Annual Meeting, Quebec, Canada, July 16, 2012

46.C. Berkland “Personal and Professional Experiences in Controlled Release”, Controlled Release Society Annual Meeting Young Investigator Award Presentation, Quebec, Canada, July 16, 2012

47.C. Berkland “Advanced Materials and Drug Delivery”, Kimberly-Clark Heritage Lecture Series, Atlanta, Georgia, May 31, 2012

48.C. Berkland “Colloids and polymers for chemical delivery”, Program of Excellence in Nanotechnology lecture series at MIT, Cambridge, Massachusetts, April 25, 2012

49.C. Berkland “Precision Particle Fabrication” Reckitt Benckiser, Hull, United Kingdom, April 11, 2012

50.C. Berkland “Precision Particle Fabrication” Kimberly-Clark, Atlanta, Georgia, April 4, 2012

51.C. Berkland “Precision Particle Fabrication” Dow Chemical, Midland, Michigan, December 7, 2011

52.J. Liang and C. Berkland “Polyelectrolyte complexes for oil and gas field applications” Schlumberger, Houston, Texas, November 14, 2011

53.C. Berkland “Engineering particles and colloids for pharmaceutical and biomaterial applications” Nagai Foundation Distinguished Lectureship for the Annual DDS Conference, Shizouka, Japan, September 15, 2011 (Keynote address)

- 54.C. Berkland “Nanoparticle Aerosol Formulations for Delivery of Current Drugs and Emerging Nucleic Acid Therapeutics” Defense Threat Reduction Agency, Washington D.C., August 1, 2011
- 55.C. Berkland “Regenerative Nanomaterials” Kinetic Concepts, Inc., San Antonio, Texas, July 11, 2011
- 56.C. Berkland “NanoCluster Technology and Microcapsule Approaches for Improved Dissolution and Solubilization” IQPC Improving Solubility Conference, Philadelphia, Pennsylvania, March 29, 2011
- 57.C. Berkland “Precision Particle Fabrication” Bioencapsulation Industrial Symposium, San Antonio, Texas, March 8, 2011
- 58.C. Berkland “Approaches for Synthesis, Formulation and Targeting of Various Contrast-Enhancing Colloids” General Electric Research Center, Albany, New York, January 6, 2011
- 59.C. Berkland “Targeted Nanomaterial Therapeutics” University of Pennsylvania, Philadelphia, Pennsylvania, January 7, 2011
- 60.C. Berkland “NanoClusters as Unique High Performance Aerosols” MAP Pharmaceuticals, South San Francisco, California, December 21, 2010
- 61.C. Berkland “Precision Particle Fabrication” Genentech, South San Francisco, California, December 21, 2010
- 62.C. Berkland “Colloids Engineered for Drug Delivery and Biomaterials Applications” University of Geneva, Geneva, Switzerland, October 22, 2010
- 63.C. Berkland “Engineering Particles: Microencapsulation and Advanced Nanoparticle Colloids” Janssen Pharmaceuticals, Beerse, Belgium, October 21, 2010
- 64.C. Berkland “Colloids Engineered for Drug Delivery and Biomaterials Applications” Eidgenössische Technische Hochschule, Zürich, Switzerland, October 19, 2010
- 65.C. Berkland “NanoClusters as Unique High Performance Aerosols” Nycomed, Konstanz, Germany, October 18, 2010

- 66.C. Berkland “Precision Particles for Controlled Release” Genentech, South San Francisco, California, September 21, 2010
- 67.C. Berkland “NanoCluster Formulation Technology” Novartis, South San Francisco, California, July 27, 2010
- 68.C. Berkland “Nanoparticle Formulation Approaches in Injectable and Pulmonary Medicines” The University of Missouri, Kansas City, Missouri, American Association of Pharmaceutical Scientists Student Chapter Distinguished Lecturer Series, May 26, 2009
- 69.C. Berkland “Particle Engineering in Aerosol and Injectable Formulations” The University of Wisconsin, Madison, Wisconsin, February 27, 2009
- 70.C. Berkland “Nanoparticles in Pulmonary Medicine” The University of Kansas Medical Center, Division of Pulmonary and Critical Care Medicine, Kansas City, Kansas, October 21, 2008
- 71.C. Berkland “Particle Engineering in Inhaled and Injectable Drug Formulations” Genentech, South San Francisco, California, July 30, 2008
- 72.J. Liang, P. Willhite and C. Berkland “Nanotechnology: From Drugs to Oil Refining” 3M Technical Forum, Minneapolis, Minnesota, June 26, 2008
- 73.C. Berkland “Translating Therapeutic Nanoparticles” Particles 2008, Orlando, Florida, May 11, 2008
- 74.C. Berkland “Pharmaceutical Applications of Nanoparticle Technology” Cima Labs, Brooklyn Park, Minnesota, August 27, 2007
- 75.C. Berkland “Engineering Nanoparticles for Biomedicine” National Institute of Standards and Technology, Gaithersburg, Maryland, May 4, 2007
- 76.M. Cordova, M. Cheng, P.G. Willhite, J. Liang, and C. Berkland “Polyelectrolyte complexes for oil and gas field applications” Conoco Phillips, Bartlesville, Oklahoma, March 13, 2007

- 77.C. Berkland “Nanoparticles for Targeted Angiogenesis: Potential Applications in Heart Disease and Spinal Cord Injury” Genentech, South San Francisco, California, November 14, 2006
- 78.C. Berkland “Engineering Pharmaceutical Nanoparticles” Globalization of Pharmaceutics Education Network, Lawrence, Kansas, October 26, 2006
- 79.C. Berkland “Nanoparticle Agglomeration for Dry Powder Formulation” Schering Plough’s Pharmaceutical Science Seminar Series in Product Development, Kenilworth, New Jersey, September 27, 2006
- 80.C. Berkland “Nanoparticle Technology in the Pharmaceutical Industry” AAPS Kansas City Discussion Group, Kansas City, Kansas, August 8, 2006
- 81.C. Berkland “Nanoclusters as a Unique Drug Delivery Platform” ACS Particles Meeting, Orlando, Florida, May 16, 2006
- 82.C. Berkland “Designing Particulate Vaccine Delivery Systems” Mannkind Corporation, Valencia, California, January 24, 2006
- 83.C. Berkland “Precision Particle Fabrication Technology” Southwest Research Institute, San Antonio, Texas, January 11, 2006
- 84.C. Berkland “Engineering Therapeutic Particles” guest lecturer in senior Biochemical Engineering course at Vanderbilt University, Nashville, Tennessee, November 7, 2005
- 85.C. Berkland “API Particle Engineering” 47th Annual International Industrial Pharmaceutical Research & Development Conference: Emerging Practices for Advancing Drug Development, Merrimac, Wisconsin, June 7, 2005
- 86.C. Berkland “Engineering micro- and nanoparticles for enhanced drug delivery performance” University of Kansas, Department of Chemistry, Lawrence, Kansas, March 7, 2005
- 87.C. Berkland “Improvements in Delivery Strategies Using Particulate Technologies to Treat Infectious Diseases” 3rd Annual Great Plains Infectious Disease Meeting, Lawrence, Kansas, September 18, 2004

Thesis Advisor and Postgraduate-Scholar Sponsor

Graduate students

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Postdoc sponsor

Bryce Stottlemire, KU, Lawrence
Kyle Apley, KU, Lawrence
Stephanie Johnson, KU, Lawrence
Jonathan Miller, KU, Lawrence
Jonathan Daniel Griffin, KU, Lawrence
Sharadvi Thati, KU, Lawrence
Madhuri Patil, KU, Lawrence
Bradly Sullivan, KU, Lawrence
Sara Thomas, KU, Lawrence
Ola Alawode, KU, Lawrence
Jun Chen, KU, Lawrence
Jian Qian, KU, Lawrence
Joshua Sestak, KU, Lawrence
Xiang Wang, KU, Lawrence
Qing Shang, KU, Lawrence
Nashwa El Gendy, KU, Lawrence
Sheng-Xue Xie, KU, Lawrence
Tatyana Yakovleva, KU, Lawrence
Huili Guan, KU, Lawrence
Azita Ahosseini, KU, Lawrence
Kristin Aillen, KU, Lawrence
Julieta Trejo, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Stephen Johnson, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Ying Ying Lin, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Parthiban Selvam, KU, Lawrence
Yasunori Iwao, University of Shizuoka, Japan
Satish Nune, KU, KU, Lawrence
Navneet Dhillon, KU Medical Center, Kansas City (co-advised with Shilpa Buch)
Lianjun Shi, KU, Lawrence
Min Huang, KU, Lawrence
Laura Peek, KU, Lawrence
Samadhi Vitharana, KU, Lawrence
Na Zhang, Associate Professor, Shandong University, China
Chadarat Duangrat, Assistant Professor, Chiang Mai University, Thailand

Lab technicians

Utkarsh Ramesh, KU, Lawrence

Jean Salash, KU, Lawrence

Jon Whitlow, KU, Lawrence

Teaching Experience

Pharmaceutical Chemistry

Fall

2006

PHCH 510 Emerging Trends in Pharmaceutical Chemistry

Fall 2008

Fall 2010

Fall 2012

Fall 2016

Fall 2018

Fall 2020

Chemical Engineering/Pharmaceutical Chemistry

Fall

2005

CPE/PHCH 715 Drug Delivery

Fall

2007

Coordinated and taught a new graduate-level course in drug delivery principles.

Fall 2009

Fall 2011

Fall 2013

Spring 2016

Spring 2017

Spring 2018

Spring 2019

Spring 2020

Spring 2021

Spring 2022

Spring 2023

Pharmaceutical Chemistry

Spring 2016

PHCH 626 Biopharmaceutics and Drug Delivery

Spring 2017

Spring 2018
Spring 2019
Spring 2020
Spring 2021
Spring 2022
Spring 2023

Chemical Engineering
Spring 2008
CPE 221 Introduction to Thermodynamics
Spring 2009

Spring 2010

Chemical Engineering
2006
CPE 111 Introduction to Chemical Engineering

Fall

Chemical Engineering
2006
CPE 800 Graduate Seminar

Fall

Chemical Engineering
Spring 2005
CPE 732 Advanced Transport Phenomena II
Spring 2006
Coordinated and taught the mass transport course to graduate students.
Spring 2007

Teaching Recognition

W.T. Kemper Fellowship for Teaching Excellence (2010)

C&PE 656 Introduction to Biomedical Engineering (2006)
Received second most votes for “best teacher” out of 12 guest lecturers for
C&PE 656. Two of these lecturers were Kemper Award winners.

Teaching Achievement Award from CPE graduate students at the CTE Celebration of Teaching (2007)

C&PE 656 Introduction to Biomedical Engineering (2008)

Received most votes for “best teacher” out of 12 guest lecturers for C&PE 656.

Professional Activities

Cystic Fibrosis Foundation Workshop panel to determine funding directives (2014)

NIH Study Sections: NHLBI Programs of Excellence in Nanotechnology, NIAID B cell Immunology Program, ETTN special emphasis on pediatric medicine, NANO

Training grants – Advisory Board; NIH NIAID – Multidimensional Vacinogenesis (past)

Advisory Board; NIH NIGMS – Pharmaceutical Aspects of Biotechnology

Journal Advisory Boards – Molecular Pharmaceutics (2021-present)

Journal of Pharmaceutical Sciences (2008-present)

Journal of Pharmaceutical Innovation (2008-2014)

Therapeutic Delivery (2009-2015)

Academic Advisory Boards – Center for Cancer Engineering, The Ohio State University

Center for Convergence of Bioscience and Medicine, University of Alabama

Kansas University Innovation Center, The University of Kansas

D3ET Research Program Steering Committee, The University of Kansas

KU Strategic Initiative Committee “Promoting Well-Being, Finding Cures”

Corporate Advising – Banner Life Sciences (2015-2017)

Dauntless Pharmaceuticals (2015-2016)

Tai'an Business Trip for Foreign Experts – One of 61 invitees traveling to Shandong, China to provide advice and collaboration opportunities for Chinese businesses.

Lawrence High School, Lawrence, KS – Technology Department Advisory Board (2006-2012). Served to develop/improve curriculum for pre-engineering training of local junior high and high schools.

Education – Director – Pharmaceutical Chemistry Undergraduate Research Program (2006-present)

Director – Education through Outreach with Lawrence High School (NSF sponsored). More than 25 high school students have conducted research at KU through this program. (2008-2013)

Director – Biomolecular Engineering Track, BioEngineering Program at KU (2010-2015)

Drug Delivery – New graduate course offering at KU

Chemical Engineering – Module for College Prep Engineering at Lawrence High School

Short course – "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceutics Education Network, Lawrence, KS

APPENDIX B

APPENDIX B - MATERIALS CONSIDERED

PETITIONS

IPR2023-00512, Paper 1, Petition for <i>inter partes</i> review of United States Patent No. 8,846,628

EXHIBITS

No.	Exhibit
1001	U.S. Patent No. 8,846,628 (“’628 patent”)
1002	Declaration of Dr. Graham Buckton (“Buckton Decl.”)
1003	Declaration of Dr. Hannah K. Batchelor (“Batchelor Decl.”)
1004	WO 2004/082619 (“Ionescu”)
1005	WO 2004/103358 (“Atadja”)
1006	Gibson, M., <i>Ch. 11, Oral Solid Dosage Forms</i> , PHARMA PREFORMULATION AND FORMULATION, CRC Press (2001) (“Gibson”)
1007	Vidaza Label 2004
1008	Vidaza Label 2007
1010	Press Release, Pharmion, “Clinical Data Presented on Pilot Pharmacokinetic Study of Oral Azacitidine” (June 2, 2007) (“Pharmion-PR”)
1011	Press Release, Pharmion, “Pharmion’s Oral Azacitidine Granted Fast Track Status for Myelodysplastic Syndromes” (August 29, 2007) (“Pharmion-PR II”)
1012	Pharmion Corporation, Form 10-K (February 29, 2008) (“Pharmion 10-K”)

No.	Exhibit
1013	Excerpts from Rowe, R.C., et al., Handbook of Pharma. Excipients, Pharma. Press, 5th ed. (2006) (“Handbook”)
1014	Chan et al., “5-Azacytidine Hydrolysis Kinetics Measured by High-Pressure Liquid Chromatography and ¹³ C-NMR Spectroscopy,” 68 (7) J Pharma. Scis. 807 (1979) (“Chan”)
1015	Kelley et al., “Furanose-Pyranose Isomerization of Reduced Pyrimidine and Cyclic Urea Ribosides,” 29 J. Med. Chem. 2351 (1986) (“Kelley”)
1016	U.S. Patent No. 3,817,980 (“Vorbruggen”)
1017	Marcucci, G., et al., “Bioavailability of Azacitidine Subcutaneous Versus Intravenous in Patients With the Myelodysplastic Syndromes,” 45 J. Clin. Pharmacology 597 (2005) (“Marcucci”)
1018	Thomson, A., “Back to basics: pharmacokinetics,” 272 Pharma. J 69 (2004) (“Thomson”)
1019	U.S. Patent Publication No. 2006/0074046 (“Redkar”)
1020	Dintaman, et al., Pharmaceutical Research, 1999, 16(10), 1550-1556 (“Dintaman”)
1021	U.S. Patent Publication No. 2004/0162263 (“Sands”)
1022	Application File History for the ’628 Patent, U.S. App. No. 12/466,213 (“File History”)
1023	U.S. Patent No. 3,350,388
1024	Pi’skala, A. and Sorm, F., COLLECT. CZECH. CHEM. COMMUN., 29, 2060-2076 (1964)
1025	Piskala, A. and Sorm, F., GB 1227691 (1971)
1026	U.S. Publication No. 2008/0057086 (“’086 Publication”) (filed as U.S. Application No. 11/849,958 (“’958 application”))

No.	Exhibit
1029	Kotke, M.K. and Rudnic, E.M, Ch. 10, Tablet Dosage Forms, MODERN PHARMACEUTICS, 4th ed. (2002) (“Modern Pharmaceutics”)
1030	Remington, <i>Ch. 45, Oral Solid Dosage Forms, and Ch. 46, Coating of Pharmaceutical Dosage Forms</i> , THE SCIENCE AND PRACTICE OF PHARMACY, 20th ed., Lippincott Williams & Wilkins (2000) (“Remington”)
1031	Dover, G.J., et al., <i>5-Azacytidine Increases HbF Production and Reduces Anemia in Sick Cell Disease: Dose-Response Analysis of Subcutaneous and Oral Dosage Regimens</i> , Blood, 66(3): 527-532 (Sep. 1985) (“Dover”)
1032	Hardy et al., Drug Delivery to the Gastrointestinal Tract, 1989 Ch. 7, 83-96 (“Hardy”)
1033	Ewe et al., Digestive Diseases and Science, 1991, 36(2) 146-152 (“Ewe”)
1034	Stoltz et al., <i>Development of an Oral Dosage Form of Azacitidine: Overcoming Challenges in Chemistry, Formulation, and Bioavailability</i> , Blood 108:4850 (2006) (“Stoltz”)
1036	U.S. Provisional Application No. 61/053,609 (“‘609 provisional”)
1037	Schwarz et al., Gastrointestinal Transit Times in Mice and Humans Measured With ²⁷ Al and ¹⁹ F Nuclear Magnetic Resonance, Magnetic Resonance in Medicine 48:255-261, 260 (2002) (“Schwarz”)
1038	Amidon et al., A theoretical basis for a Biopharmaceutic Drug Classification - The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 12:413-420 (1995) (“Amidon”)
1042	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Pharmaceutical Drugs, Vol. 50, 1990 (“IARC”)

No.	Exhibit
1045	Li et al., IV-IVC Considerations in the Development of ImmediateRelease Oral Dosage Form, J Pharma. Sci., 94(7):1396–1417 (2005) (“Li”)
1046	Obach et al., The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data, J. Pharma. & Exp. Thera., 283(1):46–58 (1997) (“Obach”)
1047	Parrott & Lavé, Prediction of intestinal absorption: comparative assessment of gastroplus™ and idea™, Euro. J. Pharma. Sci., 17:51–61 (2002) (“Parrott”)
1049	FDA Guidance for Industry, Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application, February 1987 (“PK Guideline”)
1050	U.S. Provisional Application No. 61/157,875 (“’875 provisional”)
1051	U.S. Provisional Application No. 61/201,145 (“’145 provisional”)
2003	Aparicio, A. & Weber, J., <i>Review of the clinical experience with 5-azacytidine and 5-aza-2’-deoxycytidine in solid tumors</i> , 3 CURRENT OPINION IN INVESTIGATIONAL DRUGS 627–633 (2002) (“Aparicio”)
2009	Chabner, B., et al., <i>Deamination of 5-azacytidine by a human leukemia cell cytidine deaminase</i> , 22 BIOCHEMICAL PHARMACOLOGY 2763–65 (1973) (“Chabner”)
2010	Chen, X., et al., <i>Highly Efficient Regioselective Synthesis of 5’-O-lauroyl-5-azacytidine Catalyzed by Candida antarctica Lipase B</i> , 151 APPL. BIOCHEM. BIOTECHNOL. 21–28 (2008) (“Chen”)
2011	Cheung, Y., et al., <i>Stability of azacitidine in infusion fluids</i> , 41 AM. J. OF HOSP. PHARMACY 1156–59 (1984) (“Cheung”)
2012	Čihák, A & Šorm, F., <i>Biochemical Effects and Metabolic Transformations of 5-Azacytidine in Escherichia coli</i> , 30 COLLECT. CZECH. CHEM. COMMUN. 2091–2102 (1965) (“Čihák”)

No.	Exhibit
2015	Evans, D., et al., <i>Measurement of gastrointestinal pH profiles in normal ambulant human subjects</i> , 29 GUT 1035–41 (1988) (“Evans”)
2017	Gaubert, G., et al., <i>Unnatural Enantiomers of 5-azacytidine Analogues: Syntheses and Enzymatic Properties</i> , 20(4–7) NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS 837–40 (2001) (“Gaubert”)
2018	Kaminskas, E., et al., <i>FDA Drug Approval Summary: Azacitidine (5-azacytidine, Vidaza™) for Injectable Suspension</i> , 10 THE ONCOLOGIST 176–82 (2005) (“Kaminskas”)
2020	LIEBERMAN, H., ET AL., PHARMACEUTICAL DOSAGE FORMS: TABLETS 3 (2nd Ed. 1990) 78–93, 113–20 (“Lieberman”)
2021	Lin, K., et al., <i>High -Performance Liquid Chromatographic Analysis of Chemical Stability of 5-Aza-2'-deoxycytidine</i> , 70 J. OF PHARMACEUTICAL SCI. 1228–32 (1981) (“Lin”)
2022	Mund, C., <i>Reactivation of Epigenetically Silenced Genes by DNA Methyltransferase Inhibitors: Basic Concepts and Clinical Applications</i> , 1 EPIGENETICS 7–13 (2006) (“Mund”)
2024	Notari, R. & De Young, J., <i>Kinetics and Mechanisms of Degradation of the Antileukemic Agent 5-Azacytidine in Aqueous Solutions</i> , 64 J. OF PHARMACEUTICAL SCI. 1148–57 (1975) (“Notari”)
2027	Pitřhová, P., et al., <i>Nucleic Acids Components and Their Analogues. LXVI. * Hydrolysis of 5-Azacytidine and its Connection with Biological Activity</i> , 30 COLLECT. CZECH. CHEM. COMMUN. 2801–11 (1965) (“Pitřhová”)
2028	REMINGTON, THE SCIENCE AND PRACTICE OF PHARMACY 802–938 (21st Ed. 2005) (“Remington”)

No.	Exhibit
2029	Stresemann, C. & Lyko, F., <i>Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine</i> , 123 INT. J. CANCER 8–13 (2008) (“Stresemann”)
2031	Weiss, A., et al., <i>Phase I Study of 5-Azacytidine</i> 56 CANCER CHEMOTHERAPY REP. 413–19 (1972) (“Weiss”)
2032	<i>Celgene v. Accord</i> 1:21-cv-01795-RGA Doc 40
2034	Glover, A., et al., <i>Azacytidine: 10 Years Later</i> , 71 CANCER TREATMENT REP. 737–46 (1987) (“Glover”)
2040	Ward, M., et al., <i>An oral dosage formulation of azacytidine: A pilot pharmacokinetic study</i> , J. OF CLINICAL ONCOLOGY (2007) (“Ward”)
2041	International Pat. Appl. Pub. No. WO2008/028193 (“WO2008/028193”)
2050	Deposition Transcript of Graham Buckton, Ph.D. (“Buckton Tr.”)
2052	Declaration of George M. Grass, Ph.D. (“Grass Decl.”)
2053	Declaration of William G. Blum, M.D. (“Blum Decl.”)
2054	Declaration of Jeffrey B. Etter, Ph.D. (“Etter Decl.”)
2062	Onureg [®] Label
2063	GIBSON, M., PHARM. PREFORMULATION AND FORMULATION: A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 1-11 (2001) (“Gibson Supplemental”)
2065	ALLEN, L, ET AL., ANSEL’S PHARM. DOSAGE FORMS AND DRUG DELIVERY SYS. (8th Ed. 2005) (“Ansel”)
2066	Antonsson, B., et al., <i>Effect of 5-Azacytidine and Congeners on DNA Methylation and Expression of Deoxycytidine Kinase in the Human Lymphoid Cell Lines CCRF/CEM/0 and CCRF/CEM/dCk⁻¹</i> , Cancer Research 47, 3762–78 (1987) (“Antonsson”)

No.	Exhibit
2067	AULTON, M., PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, (1988) (“Aulton”)
2070	Ben-Kasus, T., et al., <i>Metabolic activation of zebularine, a novel DNA methylation inhibitor, in human bladder carcinoma cells</i> , 70 BIOCHEM. PHARM. 121–33 (2005) (“Ben-Kasus”)
2071	Carter, J., et al., <i>Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy</i> , Signal Transduction and Targeted Therapy 5:288 (2020) (“Carter”)
2074	Covey, J., et al., <i>Differences in DNA Damage Produced by Incorporation of 5-Aza-2'-deoxycytidine or 5,6-Dihydro-5-azacytidine into DNA of Mammalian Cells</i> , 46 CANCER RESEARCH 5511–17 (1986) (“Covey”)
2076	Curtiss, F., <i>Pharmacy Benefit Spending on Oral Chemotherapy Drugs</i> , 12 J. OF MANAGED CARE PHARMACY 570–77 (2006) (“Curtiss”)
2077	DeSimone, J., et al., <i>Tetrahydrouridine, Cytidine, Analogues, and Hemoglobin F</i> , Am. J. of Hematology 18:283–88 (1985) (“DeSimone”)
2079	Case Reports, 72 BRITISH J. OF HAEMATOLOGY 467–68 (1989) (“Dunbar”)
2083	Futtermann, B., et al., <i>Studies on the Cytostatic Action Phosphorylation and Deamination of 5-Azacytidine and 5,6-Dihydro-5-Azacytidine in Hela Cells</i> , 27 BIOCHEM. PHARM. 907–9 (1978) (“Futtermann”)
2084	Garcia-Manero, G., et al., <i>Phase I Study of Oral Azacitidine in Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, and Acute Myeloid Leukemia</i> , 29 J. OF CLIN. ONCOLOGY (2011) 2521–27 (“Garcia-Manero”)

No.	Exhibit
2085	Goldin, A., et al., <i>Relation of Structure of Purine and Pyrimidine Nucleosides to Antitumor Activity</i> , 1 CANCER CHEMOTHERAPY (1968) (“Goldin”)
2087	Grønbaek, K., et al., <i>Epigenetic Changes in Cancer as Potential Targets for Prophylaxis and Maintenance Therapy</i> , 103 BASIC & CLINICAL PHARM. & TOXICOLOGY 389–96 (2008) (“Grønbaek”)
2088	Hrodek, O. & Vesely J., <i>5-Azacytidine in Childhood Leukemia</i> , 18 NEOPLASMA 493–503 (1971) (“Hrodek”)
2090	Karon, M., et al., <i>5-Azacytidine: A New Active Agent for the Treatment of Acute Leukemia</i> , 42 BLOOD 359–65 (1973) (“Karon”)
2095	Liu, H., <i>Emerging agents and regimens for AML</i> , J. HEMATOLOGY & ONCOLOGY 14:19 (2021) (“Liu”)
2096	Lomen, V., et al., “Phase I Study of 5-Azacytidine Using 24 Hrs Continuous Infusion for 5 Days” 16 PROCEEDINGS OF THE AM. ASS. FOR CANCER RESEARCH & AM. SOC. OF CLIN. ONCOLOGY (Mar. 1975) (“Lomen”)
2100	McCredie, K., <i>Treatment of Acute Leukemia with 5-Azacytidine (NSC-102816)</i> , CANCER CHEMOTHERAPY REP. 57:319–23 (1973) (“McCredieII”)
2101	Cancer Chemotherapy Reports, U.S. Dept. of Health, Edu., and Welfare (1975) (“Neil”)
2112	Shnider, B., et al., <i>A Phase I Study of 5-Azacytidine (NSC-102816)</i> , J. OF CLIN. PHARMACOLOGY 205–12 (1976) (“Shnider”)
2116	Sorm, F., et al., <i>5-Azacytidine, a New, Highly Effective Cancerostatic</i> , 20 INSTITUTE OF ORGANIC CHEM. AND BIOCHEM. 202–3 (1964) (“Sorm”)
2118	Sorrentino, V., et al., <i>Hypomethylating Chemotherapeutic Agents as Therapy for Myelodysplastic Syndromes and Prevention of Acute Myeloid Leukemia</i> , 14 PHARMACEUTICALS 641(2021) (“Sorrentino”)

No.	Exhibit
2121	Surbone, A., et al., <i>Phase I and Pharmacokinetic Study of Arabinofuranosyl-5-azacytosine (Fazarabine, NSC 281272)</i> , 50 Cancer Research 1220–25 (1990) (“Surbone”)
2123	U.S. Provisional 60/824320 File History (“60/824,320”)
2127	Vogler, W., <i>5-Azacytidine (NSC 102816): A New Drug for the Treatment of Myeloblastic Leukemia</i> , 48 Blood 331–37 (1976) (“VoglerII”)
2128	Von Hoff, D., et al., <i>5-Azacytidine A New Anticancer Drug with Effectiveness in Acute Myelogenous Leukemia</i> , 85 ANNALS OF INTERNAL MEDICINE 237–45 (1976) (“VonHoff”)
2131	Zielinski, W. & Sprinzl, M., <i>Chemical synthesis of 5-azacytidine nucleotides and preparation of tRNAs containing 5-azacytidine in its 3’-terminus</i> , 12 NUCLEIC ACIDS RESEARCH 5025–36 (1984) (“Zielinski”)
2132	Ziemba, A., et al., <i>Development of an Oral Form of Azacytidine: 2’3’5Triacetyl-5-Azacytidine</i> , CHEMOTHERAPY RESEARCH AND PRACTICE (2011) (“Ziemba”)
2143	Hirayama, H., et al., <i>Distribution and Excretion of Cyclocytidine in Monkeys, Dogs, and Rats</i> , 65 GANN 153–61 (1974) (“Hirayama”)
2144	LIEBERMAN, H., ET AL., PHARMACEUTICAL DOSAGE FORMS: TABLETS 1 (2nd Ed. 1989) (“Lieberman Vol. 1”)
2145	DEAN, D., ET AL., PHARMACEUTICAL PACKAGING TECHNOLOGY (2000) (“Dean”)
2146	GENNARO, A., REMINGTON’S PHARMACEUTICAL SCIENCES 257–309, 1519–44, 1615–32 (18th Ed. 1990) (“Remington 1990”)
2147	REMINGTON, THE SCIENCE AND PRACTICE OF PHARMACY 319–37, 702–19, 745–75, 1025–36 (21st Ed. 2005) (“Remington 2005 II”)