

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 GEORGE M. GRASS IV, PH.D.

CELGENE 2052
APOTEX v. CELGENE
IPR2023-00512

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I, George M. Grass IV, 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 President of G2 Research, Inc., a company I founded in August 2001 to provide consulting services to pharmaceutical and biotechnology companies in a variety of areas. Among other things, I have performed pharmacokinetic modeling to evaluate clinical regimens for antibodies and small molecules. I have also developed computer simulation software and models to predict drug pharmacokinetics.

4. I obtained a Ph.D. in Pharmaceutics at the University of Wisconsin, Madison in 1985. My Ph.D. thesis was entitled “Mechanisms of Corneal Drug Penetration.” As a result of this research, I was the co-recipient of the 1989 Ebert Prize, awarded by the American Pharmacists Association Academy of

Pharmaceutical Research and Sciences, for a series of manuscripts published in the Journal of Pharmaceutical Sciences entitled “Mechanisms of Corneal Drug Penetration.” I obtained an M.S. degree in Pharmaceutics at the University of Wisconsin, Madison in 1983. I obtained a Pharm. D. (clinical pharmacy) degree from the University of Nebraska in 1980 and was licensed to practice pharmacy in the state of Nebraska.

5. I have spent more than thirty years working in the pharmaceutical industry. From 1985 to 1991, I worked as a Research Scientist at Syntex Research in Palo Alto, where I was responsible for formulation development and research in oral drug absorption, including methods to orally deliver peptides. Since 1991, I have been a pharmaceutical industry consultant. In 1991, I started my own company, Precision Instrument Design Inc., and, in 1997, I started another company, NaviCyte, Inc. In 1999, NaviCyte, Inc. was acquired by Trega Biosciences, and I served as Chief Technology Officer at Trega Biosciences, Inc. until 2001. In 2001, I founded G2 Research, Inc. where I am currently the president and consult with clients on matters including pharmaceutical product and formulation development, pharmacokinetic simulation, pharmacokinetic modeling, and software development. In 2001, I also founded RaptorGraphics, Inc., a computer visualization and simulation business. From 2005 to 2007, I was Vice President of Product Development and Chief Technology Officer for PDxRx, Inc.,

a specialty-focused pediatrics company. From 2007 to 2010, I was Senior Vice President of Research and Development for Sorbent Therapeutics, Inc., a company developing novel polymer therapeutics for sodium and fluid removal in End Stage Renal Disease. From January 2016 until May 2017, I was Senior Vice President of non-clinical development and founder for NeuroVia, Inc., a company developing a novel compound for childhood cerebral adrenoleukodystrophy. From 2018 to 2022, I managed and directed the development of an oral drug product for Galera Therapeutics, Inc.

6. I developed the iDEA pharmacokinetic simulation software, a tool used to estimate absorption, distribution, metabolism, and excretion (ADME) in the pharmaceutical industry. I also maintain the iDEA affiliated databases and web sites (www.admedata.com; www.admemodel.com). I have presented numerous papers and abstracts on the iDEA software and general drug delivery at industry conferences such as the American Association of Pharmaceutical Scientists Annual Meeting and at many pharmaceutical companies throughout the world. I have also conducted drug-delivery and pharmacokinetic analyses for clinical development. I have presented the results of such analyses to FDA.

7. I am the author or co-author of more than 30 published scientific articles, primarily in the areas of models to predict drug pharmacokinetics, corneal permeability and drug transport, and intestinal transport and drug absorption. I

have authored book chapters related to drug delivery and basic pharmaceuticals and have been an invited speaker at scientific meetings. I have been a peer reviewer for a number of journals such as Pharmaceutical Research and Journal of Pharmaceutical Sciences. I am an inventor or co-inventor on eight U.S. patents and four additional U.S. patent applications and several foreign patents. My curriculum vitae is attached as **Appendix A**.

B. Compensation

8. I am being compensated at my normal consulting rate for my work, which is \$775 per hour. My compensation is not dependent on, and in no way affects, the substance of my opinions in this Declaration.

II. LEGAL PRINCIPLES

9. 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. Anticipation

10. 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.

B. Obviousness

11. 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, industry praise, 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.

12. 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.

13. 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

14. 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 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.

IV. BASIS OF OPINIONS

15. In forming my opinions set forth in this Declaration, I have considered and relied on my education and experience in the fields of pharmaceutical development, pharmacokinetics, and pharmacokinetic modeling. I have also relied on the materials listed in **Appendix B** and on a conversation with Dr. Cory Berkland.

V. BACKGROUND

A. Oral Drug Administration

16. Drugs can be administered by a variety of routes, such as intravenous injection, subcutaneous injection, and oral administration. *See, e.g.*, Ex.2067(Aulton), 3-6. In each instance, the drug must be bioavailable. Bioavailability is “a fundamental property of a pharmaceutical product for a given route of administration.” Ex.2122(Toutain), 455. “Bioavailability is understood to be the extent and the rate at which a substance or its active moiety is delivered from a pharmaceutical form, and becomes available in the general circulation.” Ex.2122(Toutain), 455 (internal quotations omitted). Intravenous injections are used to introduce substances directly into systemic circulation in the blood stream. Ex.2067(Aulton), 360. Subcutaneous injections are provided under the skin into the subcutaneous tissue where it is then absorbed into the bloodstream. Ex.2067(Aulton), 360.

17. Compared to drugs administered via intravenous or subcutaneous injections, the absorption of an orally administered drug is more complex. An oral formulation, such as a tablet, must be consumed, disintegrate to release the drug substance, be absorbed at its absorption location (typically in the upper gastrointestinal tract), and then pass into the hepatic portal system for presentation to the liver before it reaches systemic circulation in the bloodstream.

Ex.2067(Aulton), 148.

18. This process can be affected by several variables including, for example, (1) an inappropriately timed release of the drug from the formulation so the drug substance is not released from the formulation by the time it reaches its absorption location or is released early and eliminated before it reaches its absorption location; (2) decomposition of the drug in the gastrointestinal tract or formation of a non-absorbable complex of the drug so that the drug substance cannot be absorbed; (3) failure to transport the drug across the gut wall (e.g., drug permeability) so that the drug cannot be absorbed; (4) and metabolism and other elimination of the drug on the way to systemic circulation. Ex.2078(Dressman), 12; *see also* Ex.1018-0004(Thomson) (“Many factors can influence bioavailability, including the physicochemical characteristics of the drug and its formulation, the degree of first-pass metabolism in the liver or intestine, the activity of gut transporters..., the co-administration of other drugs and gastrointestinal

conditions[.]”). Because of this “the amount [of a drug] that reaches the systemic circulation is usually less than the [orally] administered dose.” Ex.1018-0004(Thomson).

19. More specifically, an oral formulation is subject to metabolism and other types of elimination mechanisms that prevent it from ever reaching systemic circulation, which include:

- acidic decomposition of the drug substance in the gastrointestinal tract (*e.g.*, the stomach) (*see* Ex.2078(Dressman), 12, 14);
- enzymatic degradation of the drug substance in the gastrointestinal tract (*see id.*, 15);
- lack of permeability leading to the drug not being absorbed (*see id.*, 12-13);
- metabolism by the gut wall (*see id.*, 12);
- metabolism by the liver (*see id.*, 12); and
- biliary excretion (*see id.*, 12).

20. The schematic below summarizes these potential elimination pathways for an orally administered drug:

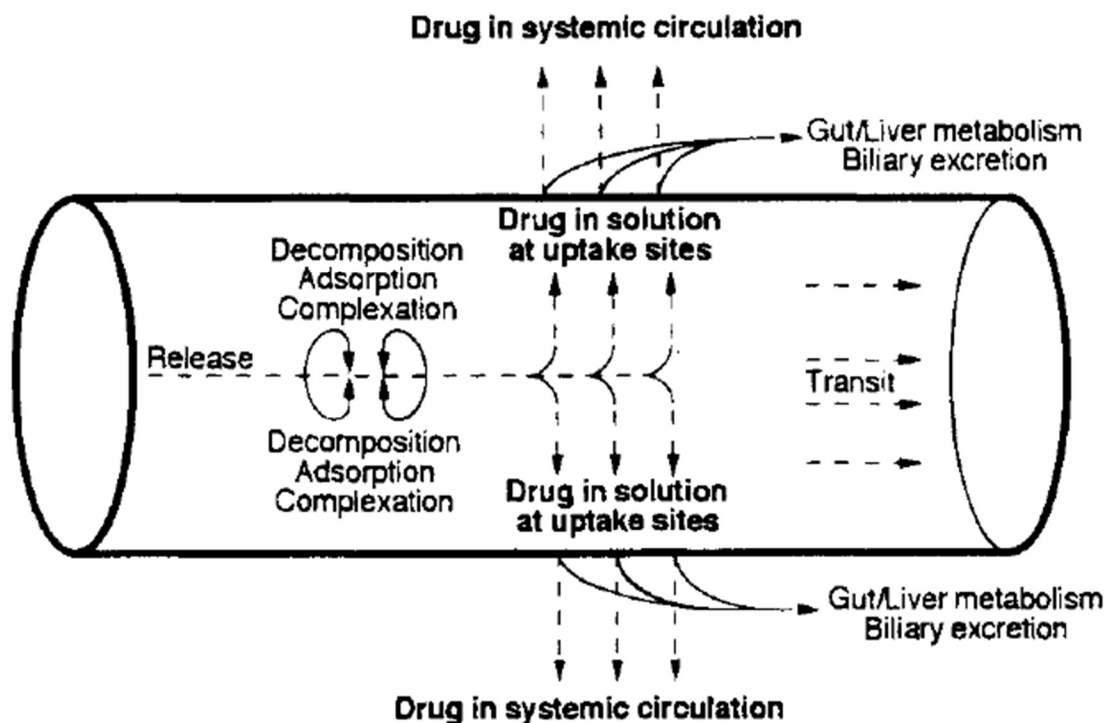


Fig. 1. Steps in drug absorption and sources of incomplete bioavailability following oral administration of a solid dosage form.

Ex.2078(Dressman), 12. As this figure suggests, the gastrointestinal tract is a dynamic system that includes drug decomposition, drug absorption, and the rate of drug movement through the gastrointestinal tract. Ex.2078(Dressman), 12.

21. As noted above, bioavailability may be affected by metabolic digestion in the liver (*e.g.*, first pass metabolism). Ex.2122(Toutain), 455. First pass metabolism of orally administered drugs that occurs presystemically is “[a] particularly important characteristic of drugs that show a high hepatic extraction ratio” that can result in “the amount of drug reaching the systemic circulation

[being] considerably less than the dose administered.” Ex.2148(Gibaldi), 332.

“Since the entire blood supply draining the upper gastrointestinal tract passes through the liver before reaching the general circulation, the fraction F of an oral dose that reaches the systemic circulation, assuming complete absorption, is given by $F = 1 - ER$ where ER is the extraction ratio.” *Id.* Thus, some drugs exhibit significantly reduced area-under-the-curve (AUC) measurements when administered orally compared to the same drug administered intravenously. *Id.* In addition, presystemic metabolism can also occur in the intestinal mucosa, further enhancing the first-pass effect. The flow chart reproduced below depicts the

course of drugs given orally and intravenously showing that orally administered drugs are subject to first pass metabolism in the gut wall and in the liver:

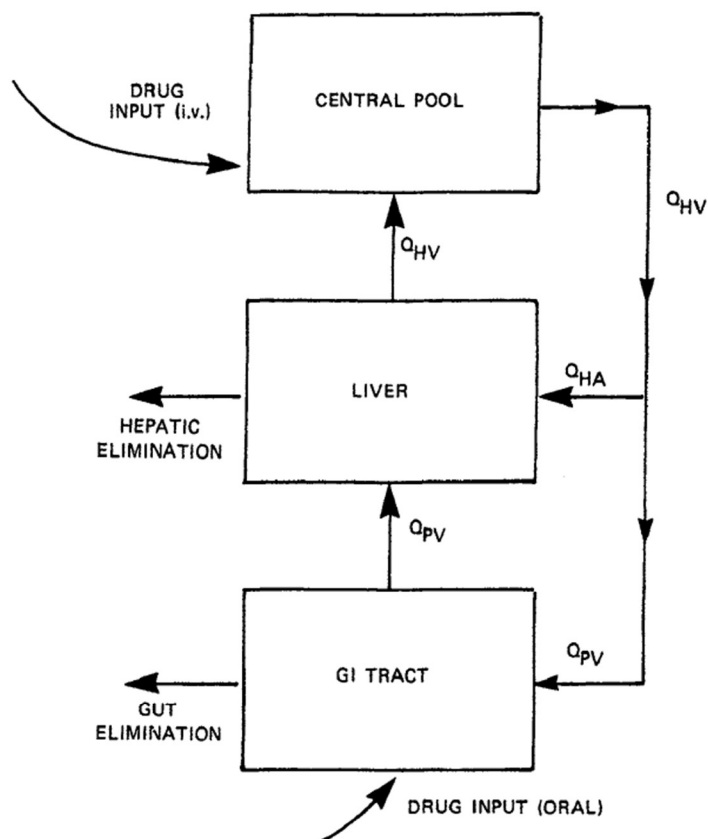


Fig. 8.7 Flow model describing the perfusion of the gastrointestinal tract and liver and showing the course of drug given orally and intravenously. After oral administration the drug is potentially subject to first-pass effects in the gut wall and in the liver. Blood flow terms are defined as follows: Q_{HV} is total hepatic blood flow, Q_{HA} is hepatic artery blood flow, and Q_{PV} is portal vein blood flow.

Id., 337.

22. These processes, in turn, affect other pharmacokinetic values, such the maximum plasma concentration (C_{max}) and time to the maximum plasma concentration (T_{max}). Ex.2122(Toutain), 462, 463. Both T_{max} and C_{max} are

influenced by the rates of drug absorption and drug decomposition.

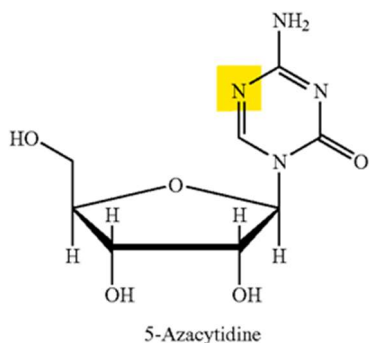
Ex.2122(Toutain), 463.

23. For all of these reasons, the bioavailability of a drug may change depending on its dosage form and path of administration. As recognized in the literature, “[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.” Ex.2067(Aulton), 133. Thus, “different formulations of the same type of dosage form or [among] different types of dosage f[or]ms” of the same drug may produce different pharmacokinetics. Ex.2067(Aulton), 133. For example, if the bioavailability of a drug administered via intravenous injection was known, one would not assume the same bioavailability for an orally administered tablet. Similarly, if the bioavailability for drug administered as an orally administered liquid was known, one would not assume the same bioavailability for an orally administered tablet, even though both are oral formulations. Incorrectly assuming that two different dosage forms or two different routes of administration will be equally bioavailable can “cause patients to be under- or overmedicated” leading to “therapeutic failure or serious adverse effects....” Ex.2067(Aulton), 133.

24. All of this would be taken into account by a POSA attempting to develop a drug product. *See, e.g.,* Ex.2078(Dressman), 11-12.

B. Overview of 5-Azacytidine

25. 5-azacytidine is an analog of the nucleoside cytidine. Ex.1001('628 patent), 2:37-38. 5-azacytidine possesses a nitrogen atom in place of a carbon atom at position 5 of cytidine's ring as highlighted in the structure below (Ex.1001('628 patent), 2:41-62):



26. I understand from conversations with Dr. Corey Berkland that although researchers synthesized 5-azacytidine in the 1960s, they struggled with developing a proper clinical formulation of 5-azacytidine for several decades due to 5-azacytidine's chemical and enzymatic instability. This understanding is further supported by my review of the '628 patent. *See, e.g.*, Ex.1001('628 patent), 3:54-56 (disclosing "oral delivery [of 5-azacytidine] prove[d] difficult due to combinations of chemical instability, enzymatic instability, and/or poor permeability"). 5-Azacytidine was approved by the FDA for *subcutaneous* injection in 2004, and for *intravenous* injection in 2007 and is marketed as Vidaza®. Ex.1007(Vidaza® Label 2004); Ex.1008(Vidaza® Label 2007).

C. The '628 Patent

27. The '628 patent is directed to “pharmaceutical compositions comprising cytidine analogs,” specifically 5-azacytidine, “for oral administration, wherein the compositions release the cytidine analog...substantially in the stomach” as well as “methods of treating diseases and disorders using the oral formulations provided.” Ex.1001('628 patent), Abstract. 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.

28. Dependent claims 11, 12, and 18-22 each depend from independent claim 1 and recite an area-under-the-curve (AUC) value (claims 11 and 12), a maximum plasma concentration ($C_{\max}$) value (claims 18 and 19), or a time to maximum plasma concentration ($T_{\max}$) value (claims 20-22). Ex.1001('628 patent), claims 11, 12, and 18-22. Each of these claims is reproduced below:

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. The composition of claim 1, which has been shown to achieve an area-under-the-curve value of at least about 400 ng-hr/mL following oral administration to a test subject.

18. The composition of claim 1, which has been shown to achieve a maximum plasma concentration of at least about 100 ng/mL following oral administration to a test subject.

19. The composition of claim 1, which has been shown to achieve a maximum plasma concentration of at least about 200 ng/mL 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.

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.

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.

29. 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.

30. Dependent claims 38-43 each depend from independent claim 28 and recite an area-under-the-curve value (claims 38 and 39), a maximum plasma concentration value (claims 40 and 41), or a time to maximum plasma concentration value (claims 42 and 43). Ex.1001('628 patent), claims 38-43. Each of these claims is reproduced below:

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.

39. The method of claim 28, which has been shown to achieve an area-under-the-curve value of at least about 400 ng-hr/mL following oral administration to a test subject.

40. The method of claim 28, which has been shown to achieve a maximum plasma concentration of at least about 100 ng/mL following oral administration to a test subject.

41. The method of claim 28, which has been shown to achieve a maximum plasma concentration of at least about 200 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.

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.

VI. THE PETITION

31. 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.

32. 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.

33. 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.

VII. THE ASSERTED REFERENCES

A. Ionescu

34. Ionescu is a patent reference that discusses the 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. “It is an object of the present invention [disclosed in Ionescu] to characterize the polymorphic forms of 5-azacytidine.” Ex.1004(Ionescu), 2:7-9.

35. Ionescu refers to injectable formulations of 5-azacytidine “slurries” suspended in a water-based solution. *See, e.g.*, Ex.1004(Ionescu), 9:11-14 (disclosing the “typically prepared” 5-azacytidine is “administered by subcutaneous injection as an aqueous suspension (‘slurry’).”), 21:24-22:6. Ionescu provides no working examples of oral 5-azacytidine administration and does not disclose any pharmacokinetic data for an oral (or any) 5-azacytidine formulation. *See*, Ex.1004(Ionescu), 15:5-22:6.

B. Atadja

36. Atadja is a patent reference that “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,” and discloses histone deacetylase inhibitors (HDAs) and their structures. Ex.1005(Atadja), Abstract; 9:15-22:5. Atadja includes 5-azacytidine as a possible chemotherapeutic agent for administration in combination with a HDAI. *See, e.g.*, Ex.1005(Atadja), 26:28-27:16. Atadja does not provides a working example of oral 5-azacytidine administration, and does not disclose any pharmacokinetic data for an oral (or any) formulation of 5-azacytidine. *See* Ex.1005(Atadja), 27-33.

C. Gibson

37. Gibson is a general textbook “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. It does not discuss 5-azacytidine.

D. PR-Press Release

38. Pharmion-PR is a press release. I understand that Pharmion was the predecessor to Patent Owner and original employer of the inventors of the '628 patent. Pharmion-PR discloses an overview of results from a pilot study “designed to assess the safety, tolerability, and pharmacokinetics of escalating single doses of orally administered Azacitidine in patients with Myelodysplastic Syndromes (MDS), acute myeloid leukemia (AML), or other solid tumors.” Ex.1010-0005(Pharmion-PR). Pharmion-PR reports 18% bioavailability relative to subcutaneous Vidaza®. Ex.1010-0005(Pharmion-PR). The study concluded, and a subsequent “multi-dose escalating study of oral azacitidine [was then] underway.” Ex.1010-0005(Pharmion-PR). Pharmion-PR does not disclose the 5-azacytidine formulation used in either study.

VIII. SUMMARY OF OPINIONS

39. In my opinion, Petitioner has failed to establish that claims 11, 12, 18-22, and 38-43 of the '628 patent are unpatentable. It is my opinion that none of these claims is unpatentable as anticipated or obvious in view of the Grounds presented by Petitioner.

40. **First**, the asserted prior art does not disclose or suggest the pharmacokinetic values of claims 11, 12, 18-22, and 38-43.

41. **Second**, the pharmacokinetic values of claims 11, 12, 18-22, and 38-43 are not the natural results of administering a formulation from, or obvious in view of, the asserted prior art.

42. **Third**, Dr. Batchelor's modeling is fundamentally flawed because a POSA would not conduct the type of analysis she performed when modeling pharmacokinetics of an oral formulation of a drug like 5-azacytidine.

43. **Fourth**, the presented extrapolation using Vidaza® pharmacokinetics and Pharmion-PR's bioavailability for Claims 11 and 38 is fundamentally flawed and should be given no weight.

44. **Fifth**, secondary considerations, *e.g.*, unexpected results, further demonstrate that the pharmacokinetic values of the non-enteric coated oral tablet formulation of 5-azacytidine are inventive, non-obvious, and patentable.

45. To the extent Petitioner argues that Dr. Batchelor’s modeling provides a motivation or a reasonable expectation of success in selecting a non-enteric coated tablet of 5-azacytidine in a therapeutically effective amount, it is my opinion that the modeling does not provide such an expectation because it is flawed.

IX. GROUND 1: IONESCU DOES NOT INHERENTLY ANTICIPATE THE PHARMACOKINETIC VALUES RECITED BY CLAIMS 11, 12, 18-22, OR 38-43.

A. Ionescu Does Not Provide Any Pharmacokinetic Values.

46. As recognized by Dr. Buckton, Ionescu does not disclose measuring pharmacokinetic data from administering a non-enteric coated tablet of 5-azacytidine to any subjects, much less the values recited in the challenged claims. *See* Ex.1004(Ionescu); Ex.2050(Buckton Tr.), 67:7-8 (“I don’t believe there are any data on administering the drug [5-azacytidine] at all” in Ionescu.). Consistent with this, Dr. Batchelor admits that she was not aware of any AUC, $C_{\max}$, or $T_{\max}$ data concerning oral administration of non-enteric coated 5-azacytidine tablets that pre-date December 2008. Ex.2049(Batchelor Tr.), 145:8-146:2. Therefore, Ionescu cannot disclose or be the natural result of the claimed pharmacokinetic limitations of claims 11, 12, 18-22, or 38-43.

B. There Is No Evidence That The Claimed Pharmacokinetic Values Are Natural Results of Administering A Formulation From Ionescu.

47. The '628 patent itself shows that pharmacokinetic values for 5-azacytidine are dose- and formulation-dependent. *See, e.g.*, Ex.1001('628 patent), Fig. 12 (depicting different pharmacokinetic area-under-the-curve values for 5-azacytidine administered as non-enteric ("F3") and enteric ("F4") formulations and administered as different doses for the same formulation); Fig. 13 (depicting different pharmacokinetic $C_{\max}$ values for 5-azacytidine administered as non-enteric ("F3") and enteric ("F4") formulations and administered as different doses for the same formulation). The pharmacokinetic properties recited in the claims result from the administration of the non-enteric coated tablet formulations disclosed in Tables 3-5 and 7 (reproduced below) at the doses disclosed in the '628 patent, *e.g.*, in Figures 12 and 13 (reproduced below). Ex.1001('628 patent), Fig. 12, Fig. 13, 73:44-58.

TABLE 7

Formulations of Azacitidine used in clinical studies		
Formulation Number	Azacitidine in Formulation	Description
#1	20 mg	"Leaky" enteric-coated tablet
#2	20 mg	Enteric-coated tablet, core sealed
#3	60 mg	Seal-coated, immediate release tablet with vitamin E
#4	60 mg	Enteric film-coated tablet, target dissolution at pH > 5.5
#5	60 mg	Enteric film-coated tablet, target dissolution at pH > 6.0
#6	60 mg	Seal-coated, immediate release tablet without vitamin E

Ex.1001('628 patent), Table 7.

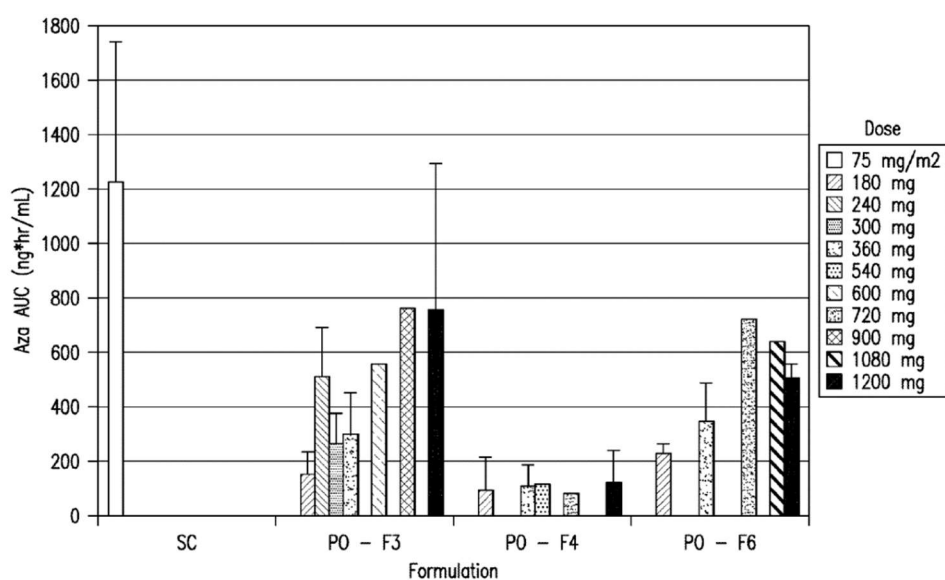


FIG. 12

Id., Fig. 12.

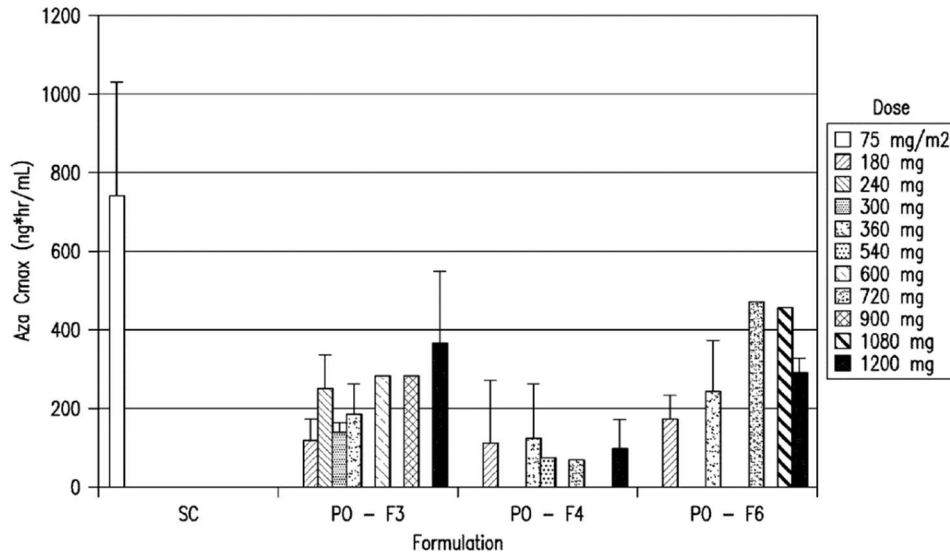


FIG. 13

Id., Fig. 13.

48. There are numerous variables of a pharmaceutical formulation that can impact pharmacokinetic values. Accordingly, two different formulations of the same drug will not necessarily produce the same pharmacokinetic values. *See e.g.*, Ex.2067(Aulton), 162. Therefore, it is my opinion that the Petitioner has not established that the alleged formulation in Ionescu necessarily or inherently results in the claimed pharmacokinetic values.

C. Dr. Batchelor's *In Silico* Modeling Is Fundamentally Flawed.

49. I understand that the Petitioner has also argued that Dr. Batchelor's *in silico* modeling demonstrates that the recited PK limitations "are necessary, natural results that follow from oral administration of Ionescu's NEC [non-enteric coated] tablet of 5-azacytidine to a test subject as disclosed by Ionescu." Pet., 29-30.

However, Dr. Batchelor's modeling is deeply flawed because a POSA would not

conduct the type of analysis she performed. Petitioner has failed to demonstrate that the claimed pharmacokinetic values are inherent to any formulation, much less the “sugar coated” tablet in Ionescu.

50. Dr. Batchelor has not approached the use of pharmacokinetic modeling software as a POSA would have in December 2008. Dr. Batchelor modeled only two specific doses without any understanding of why those doses were chosen, reason to model 5-azacytidine in this way, and with no effort to determine what factors used in the model might affect the simulated outcomes. *See e.g.*, Ex.2049(Batchelor Tr.), 33:15-34:7.

51. Dr. Batchelor admits that she was asked to perform a task and she reported the results of that task in her declaration, which was different from how modeling would typically be used by a POSA in drug development. Ex.2049(Batchelor Tr.), 37:5-38:2, 32:1-7. For example, part of Dr. Batchelor’s experience in modeling involved “scenario planning” to model “a range of situations to explore how the pharmacokinetics may be influenced by dose, [and] exploration of dose linearity, if that was required.” Ex.2049(Batchelor Tr.), 37:13-20. Dr. Batchelor also explains she has used GastroPlus to “look at the interplay of formulations in the gastrointestinal tract and the consequences on the pharmacokinetics.” Ex.2049(Batchelor Tr.), 32:1-7. In contrast to her previous

experiences, here Dr. Batchelor did not investigate any variables, but selected fixed, and largely default, values to simulate two assigned doses.

52. Indeed, Dr. Batchelor notes the vast limitation of her modeling stating that “[o]nly these two conditions were modeled, so these are the data that I’ve got. I wouldn’t really want to speculate beyond that.” Ex.2049(Batchelor Decl.), 41:7-10. This is not the approach a POSA would have taken in December 2008 when using pharmacokinetic modeling software as it leads to unreliable results for the reasons discussed below in detail.

1. Dr. Batchelor’s Modeling Ignores Metabolic Degradation Of 5-Azacytidine.

53. In December 2008 it was understood that “[t]he role of metabolism in the disposition of azacitidine is potentially quite significant.” Ex.1017-0005(Marcucci). As explained above, metabolism significantly impacts the pharmacokinetics of a drug. First, compounds that are subject to significant enzymatic degradation may exhibit non-linear pharmacokinetics, which means that one cannot assume that the kinetics of one dose will be the same as that of another dose. *See, e.g.*, Ex.2148(Gibaldi), 294 (discussing AUC and bioavailability). Secondly, orally administered compounds are subject to first pass metabolism since they encounter enzyme(s) in the gut and/or liver prior to reaching systemic circulation. *See* Section V.A. This effect is not part of the kinetics observed from intravenous or subcutaneous dosing, since drugs administered by these routes

bypass initial exposure to the gut and liver. *See* Section V.A. Thus, any pharmacokinetic values from the literature regarding intravenous or subcutaneous dosing that are used in the model do not already reflect first pass metabolism.

54. Despite these known factors, Dr. Batchelor’s modeling ignores both specific enzymatic degradation (*i.e.* by cytidine deaminase) of 5-azacytidine and general first pass metabolism in her modeling.

a. Dr. Batchelor’s modeling ignores deamination by cytidine deaminase.

55. Dr. Batchelor entirely neglects to account for enzymatic degradation of 5-azacytidine in her model, which in 2008 would have been expected to lead to different results than the modeling she conducted. By December 2008, a POSA would have understood that the ubiquitous enzyme cytidine deaminase could render 5-azacytidine biologically inactive. *See, e.g.*, Ex.2017(Gaubert), 837-838; Ex.1001(’628 patent), 3:54-56. Despite this fact, Dr. Batchelor did not account for cytidine deaminase degradation, explaining that she “didn’t think it was necessary” to consider it. Ex.2049(Batchelor Tr.), 139:11-18. Indeed, nowhere does Dr. Batchelor’s declaration mention cytidine deaminase, nor do any of the parameters she details related to oral absorption of 5-azacytidine in her model account for it. Ex.1003(Batchelor Decl.). As Dr. Batchelor acknowledges, the GastroPlus modeling software does not include cytidine deaminase degradation in its model by default. Ex.2049(Batchelor Tr.), 115:14-19.

56. To the extent that Dr. Batchelor’s modeling incorporates any enzymatic metabolism data, a POSA would understand that her modeling is limited to only enzymatic metabolism that takes place in the plasma following absorption given that her model used parameters derived from intravenous data without including the effects of presystemic enzymatic degradation. Ex.2049(Batchelor Tr.), 180:16-20 (acknowledging that “the model is constructed using the intravenous data from Marcucci” (Ex.1017) to incorporate cytidine deamination “levels in the blood”). Even Petitioner’s other expert, Dr. Buckton, acknowledged “for an oral formulation it would encounter the enzyme, I think pretty much everywhere in the body,” not *only* in the plasma. Ex.2050(Buckton Tr.), 57:1-3; *see also* Ex.2017(Gaubert), 837-838 (referring to cytidine deaminase as “ubiquitous”).

57. Dr. Buckton attempts to justify Dr. Batchelor’s decision to model enzymatic metabolism only in the plasma by suggesting, without support, that “[t]he lion’s share of [cytidine deaminase exposure] is going to be in the plasma,” “[s]o a modest exposure [to cytidine deaminase] elsewhere doesn’t sound to be like a major contributor” to loss of orally administered 5-azacytidine. Ex.2050(Buckton Tr.), 57:3-7, 57:19-58:6. A POSA would have understood that enzymatic degradation could be a significant factor in overall bioavailability. For example, Pharmion-PR demonstrates that over 80% of an orally administered 5-

azacytidine formulation is lost before entering the plasma when compared to subcutaneous administration. Ex.1010-0005(Pharmion-PR). Indeed, the literature made clear that an inhibitor of cytidine deaminase was necessary. *See, e.g.*, Ex.1019(Redkar), ¶[0233]. In view of the literature, a POSA in 2008 would understand that one possible reason for the lower oral bioavailability is due to cytidine deaminase degradation in the gastrointestinal tract. As a POSA would have understood, “[t]he best drugs can’t exert their beneficial effects if they are not reaching their target site in the body at an appropriate concentration and for a sufficient length of time.” Ex.2060(FastTrack). Because of 5-azacytidine’s established chemical and enzymatic instability as well as the limited bioavailability reported in Pharmion-PR, a POSA would not simply disregard 5-azacytidine’s exposure to cytidine deaminase before it could enter systemic circulation. Instead, a POSA constructing a reliable model would take cytidine deaminase into account.

58. Furthermore, Dr. Batchelor suggests (without having performed any analysis or modeling) that any degradation that might be happening in the gastrointestinal tract can be ignored because of very rapid transit through the intestinal tract. Ex.2049(Batchelor Tr.), 186:13-187:1. However, this is inconsistent with the fact that the small intestine transit time in GastroPlus is 3.3 hours and according to her own model the mean absorption time for 5-azacytidine is 3.142h (Ex.1003, Appendix II.A., Appendix III.A). Ex.1027(GP5.2 Manual),

51. This means that in the model, 5-azacytidine is exposed to the gastrointestinal tract and to any enzymes present in the gastrointestinal tract for over 3 hours, which a POSA would expect to play a significant role in the pharmacokinetic results.² Even if the residence time in the intestine were somehow much shorter, all of the drug absorbed from the intestine would flow from the portal vein to the liver enzymes, such as deaminase, prior to reaching systemic circulation, so a short time of absorption would not eliminate metabolic exposure prior to reaching systemic circulation. *See* Section V.A.

59. A POSA would understand that any model for orally administered 5-azacytidine must account for any deamination occurring in, for example, the stomach, the intestines, gut wall or liver *before* entering the plasma in view of the literature identifying this as a major degradation pathway. Dr. Batchelor's model did not do so. Thus, a POSA would conclude that Dr. Batchelor's modeling did not fully account for or even acknowledge the enzymatic metabolism of 5-azacytidine by cytidine deaminase. For this reason alone, it is my opinion that Dr.

² Dr. Buckton also suggests that absorption is rapid but does not provide any evidence to support this assertion. *See* Ex.2050(Buckton Tr.), 120:7-9. Based upon the knowledge of a POSA at the priority date, I do not agree with this unsupported statement.

Batchelor's model cannot be relied on to prove what would necessarily and naturally result following oral administration of 5-azacytidine.

b. Dr. Batchelor's model does not account for first pass metabolism.

60. Dr. Batchelor failed to account for "first pass metabolism," which could also affect the pharmacokinetic values output by the GastroPlus model.

61. As explained above, and as a POSA would know, all orally administered drugs absorbed in the small intestines (*e.g.*, immediate release formulations) "pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation." Ex.2067(Aulton), 148; *see also* Ex.2049(Batchelor Tr.), 125:17-22. Before entering the plasma, absorbed drugs encounter the liver, "the primary site of drug metabolism." Ex.2067(Aulton), 148; *see* Section V.A. "Extensive metabolism" may occur during this phase, causing "a significant proportion of the absorbed dose of intact drug [to] never reach the systemic circulation" and "a decrease in bioavailability...." Ex.2067(Aulton), 148.

62. A POSA would understand that GastroPlus 5.2 permits users to model this first pass effect by accounting for "the percent of drug extracted in the liver before it passes into the systemic circulation." Ex.1027-0041(GP5.2 Manual). Rather than attempting to take into account this first pass effect as a POSA would do, Dr. Batchelor assumed first pass metabolism removed *no* 5-azacytidine before entering general circulation in her modeling. *See* Ex.1003(Batchelor Decl.),

Appendix II.C, Appendix III.C (depicting Dr. Batchelor's model assuming no effect of first pass metabolism). Additionally, since Dr. Batchelor based her model on data obtained from an intravenous administration directly into the plasma, a POSA would understand that there is no possibility that the input to her model accounted for any first pass metabolism since these routes of administration specifically bypass first-pass metabolism. *See* Ex.2049(Batchelor Tr.), 109:10-16 (Dr. Batchelor acknowledging that the input data "don't report anything at all on first pass metabolism"). In fact, Dr. Batchelor did not include any rationalization on her choice to exclude first pass metabolism in her declaration.

Ex.2049(Batchelor Tr.), 103:17-104:4 ("[First pass extraction] isn't something that's covered in my declaration in detail, or at all. I don't think that I mentioned first pass in there."). Marcucci suggests to a POSA that metabolism, including first-pass metabolism, is significant for 5-azacytidine. It reports that subcutaneous and intravenous administrations of 5-azacytidine have high clearance rates suggesting that metabolism, hydrolysis, and/or degradation outside of the kidney play a significant role in 5-azacytidine's elimination. Ex.1017(Marcucci), 601.

63. First pass metabolism is a common factor affecting the observed pharmacokinetics after oral administration of a metabolized drug. *See* Section V.A. Thus, a POSA would understand that Dr. Batchelor failed to account for 5-azacytidine degradation due to first pass metabolism in her modeling, which could

play a significant role in any simulated results and/or their interpretation. This supports my opinion that Dr. Batchelor's model cannot be relied on to prove what would necessarily and naturally result following oral administration of 5-azacytidine.

2. Dr. Batchelor's model uses hydrolysis rates at a more neutral pH than that encountered by orally administered drugs.

64. While Dr. Batchelor recognized that 5-azacytidine is subject to hydrolytic degradation and attempted to account for acid-based hydrolysis of 5-azacytidine, she did not use hydrolysis rates that reflect the conditions in the stomach. Dr. Batchelor relied upon Chan (Ex.1014) providing "degradation rate constants for 5-azacytidine hydrolysis in aqueous buffer solutions at 37 °C... for various pH values between 4.5 and 8.0." Ex.1003(Batchelor Decl.), ¶¶ 34; 35-36. However, Dr. Batchelor explained her model did not adjust the hydrolysis rates for conditions beyond the range of pH values reported in the literature.

Ex.2049(Batchelor Tr.), 136:2-5 ("Based on my understanding of GastroPlus, the interpolation would direct the system to use the pH which is nearest. So it would use the data from pH 4.5 *for any pH lower than that.*" (emphasis added)). That is, Dr. Batchelor's modeling relies upon hydrolysis rates for solutions with a maximum acidity of pH 4.5, but, as Dr. Batchelor acknowledges, the pH of the stomach reaches acidic pH values of 1.1. Ex.1003(Batchelor Decl.), ¶41;

Ex.2049(Batchelor Tr.), 124:17-21. A POSA would expect that degradation would increase at more acidic pH values and recognize, that the pH of the stomach can reach roughly 2,500 times more acidic than the value relied upon in the model.

65. Because of this discrepancy, a POSA would not expect Dr. Batchelor's model to be an accurate representation of the hydrolysis rates of 5-azacytidine in the stomach. Instead, a POSA would have used a hydrolysis rate for a solution with a pH 1.1 or would have modeled a range of values to determine the parameter's criticality. Dr. Batchelor attempts to justify her inputs and suggests (without having performed any analysis or modeling) that any changes to hydrolysis rate would not affect the results because of the very rapid transit time through the stomach. Ex.2049(Batchelor Tr.), 137:19-138:9. However, Dr. Batchelor's assertion that hydrolysis rate would not affect the results of the modeling because 5-azacytidine would move quickly through the stomach runs counter to the modeling of acid hydrolysis in the first place. A POSA would have understood that the interplay of transit time and potential hydrolysis in the stomach and intestine could have been investigated in the model, but it was not. Therefore, I disagree that Dr. Batchelor has reliably accounted for degradation in the gastrointestinal tract when determining the pharmacokinetics of an oral dosage form of 5-azacytidine. *See* Ex.1003(Batchelor Decl.), ¶27.

66. I also note that Dr. Buckton provided testimony on the hydrolysis of 5-azacytidine in the acidic environment of the stomach. He incorrectly asserts that a short $T_{\max}$ indicates a rapid absorption that limits the exposure of 5-azacytidine to the acidic environment. Ex.2050(Buckton Tr.), 45:7-13. In fact, a POSA would understand that a $T_{\max}$ value is a “hybrid variable[] influenced by ***both the rate of drug elimination and absorption.***” Ex.2122(Toutain), 462 (emphasis added). A drug may show a short $T_{\max}$ because the drug is being rapidly absorbed, or it could be that the drug is being degraded prior to absorption and not absorbed, (a parallel elimination pathway). Therefore, a POSA would understand that a drug with a high elimination rate (*e.g.*, due to acid hydrolysis) may exhibit a $T_{\max}$ similar to a drug with a high absorption rate. *See, e.g.*, Ex.2122(Toutain), Fig. 8 (depicting “exactly the same $T_{\max}$ [] obtained with two different drugs... having very different rate constants of absorption” and rate constants of [preabsorptive] elimination).

67. Thus, a POSA would have understood that Dr. Batchelor does not adequately account for hydrolysis which could play a significant role in the pharmacokinetic results. For this additional reason, it is my opinion that Dr. Batchelor’s model cannot be relied on to prove what would necessarily and naturally result following oral administration of 5-azacytidine.

3. Dr. Batchelor neglected to use available experimental data.

68. Dr. Batchelor neglected to incorporate available experimental data into her modeling, which makes it less reliable than would be expected by a POSA in 2008. A POSA would understand, and Dr. Batchelor acknowledged, that it is “best practice” and “important to use experimental data where it’s available” in modeling. Ex.2049(Batchelor Tr.), 76:19-77:9; *see also id.*, 154:7-19. However, Dr. Batchelor did not input readily available real-world values when setting up her model. For example, Dr. Batchelor used an *in silico* predicted effective permeability across the intestines rather than experimentally derived permeability data. Ex.2049(Batchelor Tr.), 94:5-13 (admitting that effective permeability was generated with the ADMET Predictor), 60:2-5 (stating that the ADMET Predictor is itself a modeling program). However, measured values for permeability of 5-azacytidine were available for Dr. Batchelor’s consideration. *See, e.g.*, Ex.1026(’086 Publication), ¶[0114] (disclosing 5-azacytidine’s “measured apical to basolateral [] permeability”). Similarly, Dr. Batchelor chose to include available solubility data for pH 1.1 but not for pH 13 to build her model. *See* Ex.2049(Batchelor Tr.), 79:15-80:3, 83:2-83:12.

69. Additionally, because some of Dr. Batchelor’s inputs were generated by a separate predictor (ADMET) which generates estimated values, the reliability of her final output is further compromised by any error present in *two* modeling

programs. Ex.2049(Batchelor Tr.), 59:4-6; Ex.1027-0023(GP5.2 Manual). That is, any error in her intermediary model (*e.g.*, the ADMET Predictor) output has a direct impact on the reliability of her final model results from GastroPlus. Despite this, Dr. Batchelor provides no methodology, explanation, or even a software manual describing her use of the ADMET Predictor. There is no statement or documentation on the reliability of any predicted parameters generated by ADMET predictor. It is not clear from Dr. Batchelor's declaration whether the ADMET predictor program is capable of making accurate predictions of any parameter for 5-azacytidine.

70. Dr. Batchelor also relied upon GastroPlus's default values instead of experimental values for several required inputs. *See* Ex.1003(Batchelor Decl.), ¶¶43-46. A POSA would recognize that these "default" modeling inputs cover a number of variables, including dosage volume (Ex.2049(Batchelor Tr.), 91:4-16), particle size (Ex.2049(Batchelor Tr.), 92:5-19), mean precipitation time (Ex.2049(Batchelor Tr.), 91:21-92:1), drug particle density (Ex.2049(Batchelor Tr.), 92:5-19), prepopulated values that define the type of clinical trial to be simulated, the pKa-based solubility model, simulation length, and "other parameters" (Ex.1003(Batchelor Decl.), ¶¶43-46). Nowhere, though, does Dr. Batchelor provide any explanation or reasoning to support her reliance on the use

of these default values in place of measured values other than the fact that they exist within the program as default values.

71. A POSA would recognize that the typical use of such default values would be combined with performing parameter sensitivity analyses. Sensitivity analyses are “[a] method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions” and can aid in identifying “results that are most dependent on questionable or unsupported assumptions.”

Ex.2107(Porta), 226-227. A POSA in 2008 would perform sensitivity analyses to confirm that the default inputs did not overly influence the modeling results. *See, e.g.,* Ex.1040(Dannenfelser), 1168; Ex.1044(Keuntz), 96-97. Because Dr. Batchelor did not do so, the modeling results could vary significantly depending on the inputs and she made no attempt to determine how sensitive her modeling results were to her chosen default settings. For this additional reason, a POSA would not find the results of Dr. Batchelor’s model to be reliable or useful in any way and therefore cannot be relied on to prove what would necessarily and naturally result following oral administration of 5-azacytidine.

4. Dr. Batchelor did not perform any model validation.

72. In addition to not performing sensitivity analysis, Dr. Batchelor did not perform any other validation of her modeling. A POSA would recognize

this lack of validation as being contrary to the standard in the field of pharmacokinetic modeling.

73. By 2008 physiologically based pharmacokinetic “model validation on each of the key input parameters... remains the recommended strategy for human modeling.” Ex.1039(Buck), 1779-1780; Ex.1044(Kuentz), 96 (the “usual strategy with GastroPlus™ is therefore to verify the simulations against in vivo results in one or more preclinical species” because “the complexity of the GastroPlus™ model and the numerous input data”). In fact, Dr. Batchelor appropriately uses validation metrics in her academic work. *See* Ex.2049(Batchelor Tr.), 159:22-160:5; Ex.2048(Pawar), 5.

74. In the 5-azacytidine modeling, however, Dr. Batchelor did not perform any validation to demonstrate that her model was reliable in any way despite the several shortcomings discussed above. For example, Dr. Batchelor never compared her modeled results to measured values. *See* Ex.2049(Batchelor Tr.), 14:22-143:18, 143:21-144:14, 143:15-144:6. A POSA would understand that without conducting any appropriate validation, Dr. Batchelor’s modeling cannot be considered any more than a mere, dubious possibility. For this additional reason, a POSA would not rely on a model such as the one provided by Dr. Batchelor, to prove what would necessarily and naturally result following oral administration of 5-azacytidine.

D. Conclusion for Ground 1

75. In summary, Dr. Batchelor repeatedly ignores known critical parameters (*e.g.*, first pass metabolism and non-linear kinetics) and instead chooses default parameters. Dr. Batchelor claims this is because “there was no data to be included....” Ex.2049(Batchelor Tr.), 105:20-106:5. However, this is not how a POSA would approach *in silico* pharmacokinetic modeling of an oral dosage form. Rather, a POSA would recognize that without such important data reflecting a compound’s known behavior, reliable modeling cannot be achieved. Thus, until the necessary data is available, the approach cannot be warranted.

76. For at least these reasons, a POSA would recognize Dr. Batchelor’s testimony as unsupported, incomplete, and unreliable. As such, my opinion is that Ionescu does not anticipate any of claims 11, 12, 18-22, or 38-43 because the modeling cannot demonstrate that the pharmacokinetic values recited in any of claims 11, 12, 18-22, or 38-43 are inherently anticipated.

X. CLAIMS 11, 12, 18-22, AND 38-43 OF THE ’628 PATENT ARE NOT INHERENTLY OBVIOUS IN VIEW OF IONESCU IN COMBINATION WITH ATADJA, GIBSON AND THE KNOWLEDGE OF A POSA (GROUND 2).

77. I understand that Petitioner has argued that the combination of Ionescu (Ex.1004), Atadja (Ex.1005), Gibson (Ex.1006), and the knowledge of a POSA would have made each of claims 11, 12, 18-22, and 38-43 inherently obvious. I disagree.

A. None of Ionescu, Atadja, Or Gibson Provide Any Pharmacokinetic Values.

78. As discussed above, nowhere does Ionescu (Ex.1004) disclose any pharmacokinetic values whatsoever including those recited in the above claims. *See* Sections VII.A, IX.A. Likewise, as discussed previously in the summary of the references, neither Atadja (Ex.1005) nor Gibson (Ex.1006) disclose the claimed pharmacokinetic values. As with Ionescu, none of these references discloses measuring pharmacokinetic values for 5-azacytidine, let alone for a non-enteric coated tablet comprising a therapeutically acceptable amount of 5-azacytidine. Thus, none of Ionescu, Atadja, and Gibson disclose the pharmacokinetic limitations recited in claims 11, 12, 18-22, or 38-43.

B. There Is No Evidence That The Claimed Pharmacokinetic Values Are Natural Results of Administering The Alleged Obvious Formulation.

79. As discussed above, *see* Sections VII.A-C, IX.B, it is my opinion that the Petitioner has not established that the alleged prior art formulation necessarily or inherently results in the claimed pharmacokinetic values because the prior art formulation is not the same as the formulation that resulted in the claimed pharmacokinetic values.

C. Dr. Batchelor's *In Silico* Modeling Is Fundamentally Flawed.

80. As discussed above, *see* Section IX.C, it is my opinion that a POSA would recognize Dr. Batchelor's testimony as unsupported, incomplete, and

unreliable. The modeling in no way demonstrates that the pharmacokinetic values recited in any of claims 11, 12, 18-22, or 38-43 are inherently obvious and it should be given no weight.

81. For the same reasons as discussed above, *see* Section IX.C, a POSA would not rely on Dr. Batchelor's modeling for providing a motivation to select a non-enteric coated tablet formulation of 5-azacytidine or provide a POSA a reasonable expectation of success because a POSA would recognize Dr. Batchelor's analysis as unreliable. Despite Dr. Buckton's characterization of Dr. Batchelor's pharmacokinetic results as confirming an "acceptable bioavailability" (Ex.1002(Buckton Decl.), ¶119), a POSA would not have been able to reach such a conclusion without the benefit of the experimental data first disclosed in the '628 patent demonstrating this. *See, e.g.*, Ex.1001('628 patent), Fig. 10, Fig. 12, Fig. 13, Fig. 14, Fig. 15, Fig. 16, 71:9-18, 72:39-52, 72:44-58, 73:1-8, 73:22-32, 73:59-74:23, 66:50-67, Table 7, Table 8, Table 10. As of December 2008, a POSA would have understood that FDA-approved Vidaza® dosed at 75mg/m² results in an AUC and C_{max} for of 960.53±458.06 and 750±403, respectively. *See* Ex.1017-0004(Marcucci); Ex.1007-0009(Vidaza® Label 2004). A POSA would have recognized that such results are well above the values predicted by Dr. Batchelor's model. Furthermore, Ward discloses that there is a "complex, non-linear relationship between plasma exposure and pharmacodynamic effect of azacitidine"

that needs to be explored for an oral formulation. Ex.2040(Ward). That is, without the disclosure of the '628 patent, a POSA would not have had any expectation that the pharmacokinetic values predicted for a non-enteric coated tablet by Dr. Batchelor would be therapeutically effective.

D. Extrapolation using Vidaza® pharmacokinetics and Pharmion-PR's bioavailability for Claims 11 and 38 Is Fundamentally Flawed.

82. Petitioner states that “a POSA would have expected that a dose of 200 mg or more of 5-azacytidine... would have satisfied the AUC limitations of Claims 11 and 38 (AUC of ‘at least about 200 ng-hr/mL’) based on reported PK properties of oral tablets containing 80 mg of 5-azacytidine” including a bioavailability of 18% relative to subcutaneous administration. Pet., 52. Petitioner additionally states that “a POSA would have understood that AUC typically increases with increasing dose” such that a POSA would expect increasing the dose “would have likely further increased [the] AUC....” *Id.*, 52-53.

83. It is my opinion that Petitioner is incorrect and makes multiple errors in this assessment.

84. First, none of the references cited in the Petition disclose “oral tablets containing 80 mg of 5-azacytidine.” *See* Ex.1004(Ionescu); Ex.1005(Atadja); Ex.1006(Gibson); Ex.1010(Pharmion-PR); *see* Section VII.A-D. It appears that Petitioner is relying on Pharmion-PR, but as Dr. Buckton correctly notes,

Pharmion-PR “doesn’t specifically say tablet, I believe.” Ex.2050(Buckton Tr.), 90:13-19.

85. Additionally, the Petition’s calculations are incorrect. The Petition states that “[b]ased on the[] disclosures” of Pharmion-PR(Ex.1010), Marcucci(Ex.1017), and the Vidaza Label 2007(Ex.1008) “a POSA would have understood that the 80 mg oral dose had an AUC of approximately 172.9 ng-h/mL (i.e., 18% of SC Vidaza’s AUC, 960.53 ng-h/mL).” Pet. 52; *see also* Ex.1002(Buckton Decl.), ¶¶164-167. Petitioner and Dr. Buckton appear to have simply calculated 18% of the 960.53 ng-h/mL AUC value. This approach incorrectly fails to account for the differences between the oral dose in Pharmion-PR and the subcutaneous dose in Marcucci. Marcucci’s 960.53 ng-h/mL AUC value results from administering a 75 mg/m² dose to patients with a mean body surface area of 1.9 ± 0.2 m². Ex.1017-0004(Marcucci), Table 1. Thus, Marcucci’s AUC is for a set of patients receiving on average 142.5 mg 5-azacytidine (*i.e.*, 75mg/m² × 1.9m²). Thus, even if a POSA were to use Marcucci’s data to attempt to calculate the AUC of the 80mg dose in Pharmion-PR, after properly accounting for Marcucci’s dose the calculated AUC would be only 97.4 ng-h/mL $\left(\left(\frac{80\text{mg}}{142.5\text{mg}} \right) \times 960.53 \right) \times 18\%$ — less than half of the “at least about 200 ng-hr/mL” recited in claims 11 and 38. Thus, a POSA would **not** conclude that the

disclosure of an 80 mg dose satisfies the AUC limitation of Claims 11 and 38 as put forth by Petitioner and Dr. Buckton, at least because the correct calculations demonstrate this is mathematically false. Pet., 52; Ex.1002(Buckton Decl.), ¶166.

86. Further, even if doses were altered, a POSA would understand that it is incorrect to assume that a bioavailability of an 80mg dose of unknown formulation would remain constant across other doses or would be broadly applicable to other formulations. *See e.g.*, Ex.2049(Batchelor Tr.), 48:3-13. This incorrect assumption leads to Petitioner's unsupported conclusion that AUC would increase proportionally with increasing dose.

87. In fact, the '628 patent's disclosure itself demonstrates the error in this assumption. For example, the '628 patent states that the AUC of a non-enteric, "[s]eal-coated, immediate release tablet without vitamin E" "was not proportional with [the] dose." Ex.1001-0060('628 patent), Table 7, -0062; *see also* Ex.1001-0061 ("Plasma PK profiles following... various PO doses are compared and presented in FIG. 3. An increase in oral dose did not result in dose-proportional increase in exposure [to] azacitidine."); Figure 3; -0063; Table 7. Further, a POSA would recognize that the '628 patent's pharmacokinetic measurements demonstrate that **increasing** doses lead to **decreasing** bioavailability. Figure 14, annotated and reproduced below, demonstrates this non-linear relationship:

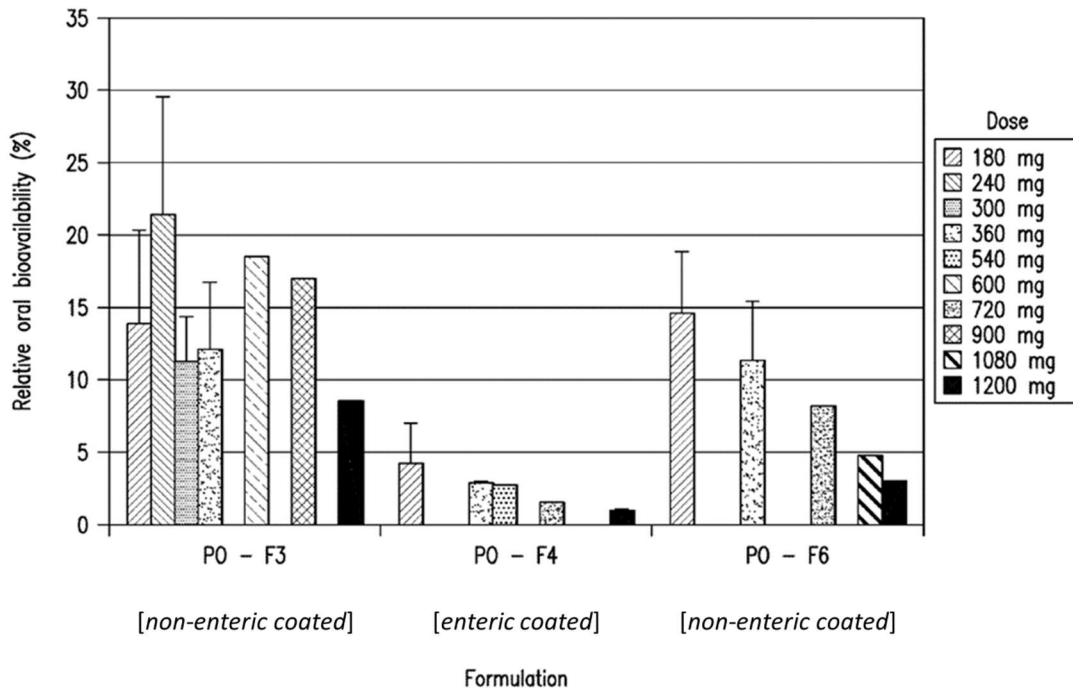


FIG. 14

Ex.1001('628 patent), Fig. 14; *see also id.*, -0063; Table 7.

88. Petitioner and Dr. Buckton and Dr. Batchelor have no evidence that oral bioavailability would have been expected to remain the same at higher doses and for a non-enteric coated tablet formulation of 5-azacytidine. It is my opinion, therefore, that this argument also fails to render claims 11 and 32 obvious.

E. Conclusion for Ground 2

89. For at least these reasons, it is my opinion that Ionescu, Atadja, Gibson and the knowledge of a POSA do not render obvious any of claims 11, 12, 18-22, and 38-43.

XI. CLAIMS 11, 12, 18-22, AND 38-43 OF THE '628 PATENT ARE NOT OBVIOUS IN VIEW OF IONESCU IN COMBINATION WITH ATADJA, GIBSON, PHARMION-PR, AND THE KNOWLEDGE OF A POSA (GROUND 3).

90. I understand that in Ground 3, Petitioner does not point to any additional arguments for claims 11, 12, 18-22, or 38-43 as compared to Ground 2.³ Pet. 58-59. Therefore, I disagree for the same reasons provided for Ground 2. *See* Section X. Further, the pharmacokinetics and pharmacodynamic effects of oral 5-azacytidine remained unknown at the time (Ex.1011(Pharmion-PR II)), which also suggested that a POSA would not have had a reasonable expectation of success in pursuing a non-enteric coated tablet. For at least these reasons, it is my opinion that Ionescu, Atadja, Gibson, Pharmion-PR and the knowledge of a POSA do not render obvious any of claims 11, 12, 18-22, and 38-43.

XII. OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS OF CLAIMS 11, 18, 38, AND 40 OF THE '628 PATENT

³ Like Ionescu, Atadja, and Gibson, Pharmion-PR fails to disclose the claimed pharmacokinetic values. Pharmion-PR is a press release that only discloses the “relative” bioavailability of an oral formulation of 5-azacytidine (*see* Ex.1010-0005(Pharmion-PR); *see* Section VII.D), but nowhere does it disclose the pharmacokinetic values recited in any claims.

91. 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.

92. I have been informed that Dr. Berkland has opined on several objective indicia including long-felt, unmet need, skepticism of others, unexpected results, and industry praise related to independent claims 1 and 28. I further understand that these objective indicia equally apply to claims depending from claim 1 (including claims 11, 18, and 20-22), or depending from claim 28 (including claims 38, 40, 42, and 43). In my opinion, additional objective indicia (*e.g.*, unexpected results) are relevant for dependent claims reciting pharmacokinetic values.

A. The pharmacokinetic values recited by claims 11, 18, 38, and 40 were unexpected for a non-enteric coated tablet comprising a therapeutically effective amount of 5-azacytidine.

93. Because of the well-established belief that 5-azacytidine was susceptible to hydrolysis and chemically unstable in acidic environments, was enzymatically labile, and was poorly permeable, there was substantial skepticism in the field facing a non-enteric oral formulation. *See, e.g.*, Ex.1021(Sands). Because of the known issues with 5-azacytidine's stability, oral formulations focused primarily on *enteric* coated formulations that would protect the drug from hydrolysis, acid degradation, and enzymatic decomposition so that favorable pharmacokinetic results could be achieved. *See* Ex.1021(Sands), ¶¶[0012], [0029]-[0030]; Ex.2041(WO2008/028193). Because of these prejudices, a POSA would not have expected a non-enteric formulation of 5-azacytidine for oral administration to achieve therapeutic pharmacokinetic values. However, the non-enteric coated 5-azacytidine tablet of the claims exhibited unexpectedly impressive pharmacokinetic, pharmacodynamic, and clinical properties.

94. Despite being exposed to the acidic gastric environment, and aqueous and enzymatically active gastrointestinal environment, non-enteric coated tablets of 5-azacytidine unexpectedly provided more favorable pharmacokinetic measurements than the same composition administered with an enteric coating to provide protection from the stomach and to deliver the drug to its understood site

of absorption in the intestine.⁴ Compared to enterically coated tablets, non-enteric coated tablets of 5-azacytidine resulted in **higher** $C_{\max}$ measurements (Ex.1001('628 patent), Fig. 13, Fig. 10, -0063, Table 7), **greater** AUC values (*id.*, Fig. 12, 72:39-52, 72:44-58, 73:1-8, 74:4-16), and therefore **higher** bioavailability (*id.*, Fig. 14, Fig. 15, 73:59-74:16). Thus, contrary to expectations the protective enteric coating did not enhance performance of 5-azacytidine.

95. Thus, starting with a known drug which was also long known to have properties incompatible with oral administration, a POSA could not have expected to arrive at the pharmacokinetic values recited in claims 11, 18, 38, or 40 with a non-enteric coated tablet formulation.

⁴ My opinion would not change, even if Ionescu (Ex.1004) is considered the closest prior art to which the invention's pharmacokinetic values must be compared. As discussed previously, nowhere does Ionescu (Ex.1004) (or Atadja (Ex.1005), Gibson (Ex.1006), or Pharmion-PR (Ex.1010)) provide any pharmacokinetic values. *See* Sections VII.A-D. For at least these reasons, a POSA would not have expected the pharmacokinetic values of the invention from a non-enteric coated tablet of 5-azacytidine based on the compendium of literature in the field.

B. Nexus

96. 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. I understand Dr. Berkland has opined on nexus as it relates to the challenged claims and concluded that Onureg® embodies and is coextensive with at least claims 11, 18, 38, and 40.

97. These additional secondary considerations strongly indicate that challenged claims 11, 18, 38, and 40 are non-obvious.

XIII. CONCLUSION

98. For the above reasons, it is my opinion that Petitioner has not demonstrated that any of claims 11, 12, 18-22, and 38-43 of the '628 patent are anticipated or obvious.

XIV. AVAILABILITY FOR CROSS-EXAMINATION

99. 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

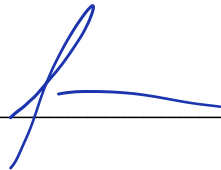
cross examination within the United States during the time allotted for cross examination.

XV. RIGHT TO SUPPLEMENT

100. 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

101. 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. George M. Grass IV

Date: 10/11/2023

APPENDIX A

Curriculum Vitae
George M. Grass IV

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EDUCATION

- August, 1985: Ph.D. Pharmaceutics. University of Wisconsin, Madison, Wisconsin. Thesis title: Mechanisms of Corneal Drug Penetration.
- 1980-1983: MS Pharmaceutics. University of Wisconsin, Madison, Wisconsin. Thesis title: Relationship of Chemical Structure to Corneal Penetration for Small Organic Compounds.
- 1977-1980: Pharm.D. University of Nebraska Medical Center, Omaha, Nebraska. Licensed to practice pharmacy in Nebraska.
- 1975-1977: Pre-Med/Pharmacy, University of Nebraska, Lincoln, Nebraska.

EXPERIENCE

- August 2001 – Present: President G2 Research, industry consultant to drug discovery and biotechnology organizations and investors. Development and licensing of iDEA® pharmacokinetic simulation software and databases (www.admedata.com, and www.admemodel.com).
- January 2016 – May 2017: Sr. Vice President of Non-Clinical Development and Founder NeuroVia, Inc. Responsible for execution of all non-clinical development functions for a novel treatment of a pediatric orphan disease including: Formulation development, manufacture of clinical supplies, toxicity testing, bioanalytical, preparation of relevant information for FDA submissions. Other responsibilities including corporate strategy, planning and execution, communication to potential and current investors.
- Aug 2007 - Aug 2010: Sr. Vice President of Research and Development, Sorbent Therapeutics, a company developing novel therapeutics for sodium and fluid removal. Responsibilities including: corporate strategy, planning and execution; identification, evaluation, integration and management of outside technologies and services. Develop novel technology and product formulation strategy. Assist in representing the company to potential partners and investors and FDA.
- May 2005 – Mar 2007: Vice President of Product Development and Chief Technology Officer, PDxRx Inc. a subspecialty focused pediatrics company. Responsibilities including: corporate management and strategy; identification and negotiation of new product/technology opportunities. Assist in representing the company to potential partners and investors.
- 1999-August 2001: Chief Technology Officer, Corporate Officer, Trega Biosciences (acquired by Lion bioscience 4/2001) – corporate management and strategy; identification, evaluation and negotiation of outside technologies; technical development of iDEA® pharmacokinetic simulation software; presentation of corporate technology and strategy to and negotiation with customers, collaborators, scientific community and current and prospective investors.
- 1997-2008: Founder and Vice President RaptorGraphics, Inc., Seattle WA (acquired by MDE Engineering Inc.). Corporate management and technical / strategic development of computer graphics and simulation business targeted to legal applications.

- 1996-1999: Founder, President, CEO and Chief Business Officer, NaviCyte, Inc. (acquired by Trega Biosciences 11/1999) – Responsible for all corporate/financial/strategic management and establishment of all contracts/licenses. Design of new products, establishment of contract service organization, development of simulation models to predict pharmacokinetics and pharmacodynamics. Establishment of Pharma consortium for development of ADME simulation software.
- 1987 -1996: Founder, President and CEO of Precision Instrument Design, Inc., Tahoe City, CA. Design, manufacture, and marketing of laboratory equipment for conducting basic research in drug delivery. Responsible for all corporate/financial/strategic management. Development of simulation models to predict pharmacokinetics and pharmacodynamics.
- 1991 - 1996: Pharmaceutical industry consultant on drug delivery subjects including oral delivery, controlled release, peptide and protein delivery, ocular drug delivery and simulation modeling of various drug delivery related issues.
- 1985-1991: Staff Researcher I / II, Pharmaceutical Development, Dosage Design and Development, Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, California. Development of early stage (pre IND, IND and pre NDA) compounds for oral delivery. Basic research in mechanisms of oral absorption including methods to orally deliver peptides. Computer modeling and pharmacokinetic simulations. Supervision of two BS/MS positions, one Post Doctoral Fellow and various interns.
- 1983-1985: Computer sales and installation, CBM Computer Center, Madison, Wisconsin. Sales and installation of microcomputers. Network installations and troubleshooting.
- 1980-1985: Teaching (Pharmaceutics and Pharmaceutical Dispensing laboratory classes) / Research Assistant, University of Wisconsin, Madison, Wisconsin.
- 1980: Research Technician, Creighton University, Omaha, Nebraska. Fabrication of gels and matrices from various polymers for ocular inserts. Conducted ocular pharmacokinetic determinations using measurements of miosis in rabbits.
- 1977-1979: Research Technician, Product Development, Streck Laboratories, Omaha, Nebraska. Developed methods for fixation, cryoprotection of platelets and red blood cells. Product development of latex calibration standards for various cell counters.

AWARDS, HONORS, AFFILIATIONS

Co-recipient 1989 Ebert Prize
 Sigma Xi Scientific Research Society
 Rho Chi Pharmacy Honor Society
 Member, American Association Pharmaceutical Sciences
 Member, Controlled Release Society

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APPENDIX B

APPENDIX B - MATERIALS CONSIDERED PETITIONS

IPR2023-00512, Paper 1, Petition for <i>inter partes review</i> 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, <i>Clinical Data Presented on Pilot Pharmacokinetic Study of Oral Azacitidine</i> (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”)
1014	Chan et al., <i>5-Azacytidine Hydrolysis Kinetics Measured by High-Pressure Liquid Chromatography and 13C-NMR Spectroscopy</i> , 68(7) J. PHARMA. SCIS. 807 (1979) (“Chan”)

No.	Exhibit
1017	Marcucci, G., et al., <i>Bioavailability of Azacitidine Subcutaneous Versus Intravenous in Patients with the Myelodysplastic Syndromes</i> , 45 J. CLIN. PHARMACOLOGY 597 (2005) (“Marcucci”)
1018	Thomson, A., “Back to Basics: Pharmacokinetics,” 272 PHARMA. J. 769 (2004) (“Thomson”)
1019	U.S. Patent Publication No. 2006/0074046 (“Redkar”)
1021	U.S. Patent Publication No. 2004/0162263 (“Sands”)
1026	U.S. Publication No. 2008/0057086 (“’086 Publication”) (filed as U.S. Application No. 11/849,958 (“’958 application”))
1027	GastroPlus version 5.2 Manual (“GP5.2 manual”)
1039	Buck et al., <i>Prediction of Human Pharmacokinetics Using Physiologically Based Modeling: A Retrospective Analysis of 26 Clinically Tested Drugs</i> , DRUG METABOLISM & DISPOSITION, 35(10):1766–1780 (2007) (“Buck”)
1040	Dannenfelser et al., <i>Development of Clinical Dosage Forms for a Poorly Water Soluble Drug I: Application of Polyethylene Glycol–Polysorbate 80 Solid Dispersion Carrier System</i> , J PHARMA. SCI., 93(5):1165–1175 (2004) (“Dannenfelser”)
1041	Press Release, Simulations Plus, Inc., “Simulations Plus Releases GastroPlus™ 5.2” (Nov. 30, 2006) (“GP5.2 PR”)
1042	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Pharmaceutical Drugs, Vol. 50, 1990 (“IARC”)
1043	Israili et al., The Disposition and Pharmacokinetics in Humans of 5-Azacitidine Administered Intravenously as a Bolus or by Continuous Infusion, Cancer Res. 36:1453-1461 (1976) (“Israili”)
1044	Kuentz et al., <i>A strategy for preclinical formulation development using GastroPlus™ as pharmacokinetic simulation tool and a</i>

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	<i>statistical screening design applied to a dog study</i> , EURO. J. PHARMA. SCI., 27:91–99 (2006) (“Kuentz”)
1045	Li et al., IV-IVC Considerations in the Development of Immediate-Release 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”)
1048	Simulations Plus, Inc., Form 10-QSB (January 16, 2007) (“SLP 10-QSB”)
1052	The SDF file for the PubChem compound entry for Azacitidine (PubChem CID 9444) (September 16, 2004) (“Conformer3D_CID_9444 (1).sdf”), printed to PDF
1053	ADMET Predictor Output file (“Azacitidine ADMET.txt”), printed to PDF
1054	CDD file for 200 mg dose (“Azacitidine 200 mg.cdd”), printed to PDF
1055	IV plasma concentration-time data file for 200 mg dose (“Azacitidine 200 mg.ipd”), printed to PDF
1056	Result data file for 200 mg dose (“Azacitidine 200 mg All Data.txt”), printed to PDF
1057	CDD file for 400 mg dose (“Azacitidine 400 mg.cdd”), printed to PDF
1058	IV plasma concentration-time data file for 400 mg dose (“Azacitidine 400 mg.ipd”), printed to PDF

No.	Exhibit
1059	Result data file for 400 mg dose (“Azacitidine 400 mg All Data.txt”), printed to PDF
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”)
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2048	Pawar, et al., <i>Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: A Carbamazepine Case Study</i> , 25 AAPS J. 67 (2023) (“Pawar”)
2049	Deposition Transcript of Hannah K. Batchelor (“Batchelor Tr.”)
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2107	PORTA, M., A DICTIONARY OF EPIDEMIOLOGY 226–27 (5th Ed. 2008) (“Porta”)

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2122	Toutain, P. & Bousquet-Melou, A., <i>Bioavailability and its assessment</i> , 27 J. VET. PHARMACOLOGY. THERAP. 455–66 (2004) (“Toutain”)
2148	GIBALDI, M. & PERRIER, D., PHARMACOKINETICS (2nd Ed. 2007) 271–353 (“Gilbaldi”)