

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 JEFFREY ETTER, PHD

CELGENE 2054
APOTEX v. CELGENE
IPR2023-00512

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I, Jeffrey B. Etter, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Celgene Corporation (“Patent Owner”) in connection with *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 am a named inventor on ’628 patent, along with my former colleagues at Pharmion Dr. Mai Lai and Dr. Jay Thomas Backstrom. Ex.1001(’628 patent). I understand that Apotex Inc. (“Apotex”) has 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. I have been asked to explain how I and my co-inventors developed the inventions described in the ’628 patent.

3. I am being compensated for my time in connection with this matter at my standard consulting rate, which is \$275.00 per hour. My compensation is not dependent in any way upon the substance of my testimony or the outcome of this matter.

II. QUALIFICATIONS AND EXPERIENCE

4. I earned my bachelor’s degree with a major in chemistry from Franklin & Marshall College in 1982. I earned my Ph.D. in organic chemistry from the University of Colorado in 1987.

5. Since earning my Ph.D., I have spent over 30 years in the drug development industry, holding positions as Director of Analytical Development at Somatogen (1990-1998), VP of Manufacturing at RxKinetic (1998-2002), Director of Drug Product at Allos Therapeutics (2002-2004), Director of Drug Product at Pharmion (2005-2008), Director of Formulations at Celgene (2008-2009), and Director, Senior Director, VP, and Senior VP of Pharmaceutical Development at Clovis Oncology (2009-2023). This year, I formed and am the managing member of Etter CMC Consulting, LLC where I consult for various clients on the production and development of drug products.

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

III. BASIS OF OPINIONS

7. I have considered the materials listed in **Appendix B**.

IV. THE DEVELOPMENT OF NON-ENTERIC COATED TABLETS COMPRISING A THERAPEUTICALLY EFFECTIVE AMOUNT OF 5-AZACYTIDINE

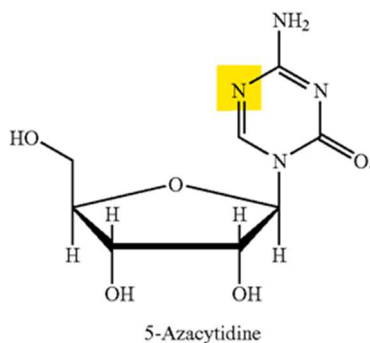
8. I was hired by Pharmion in 2004 to develop an oral formulation of 5-azacytidine to treat myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML or acute myelogenous leukemia). I worked closely with Dr. Mei Lai to develop oral formulations of 5-azacytidine, while Dr. Backstrom spearheaded the

clinical trials. Our work resulted in the inventions described in the '628 patent and the FDA-approved drug Onureg®. I describe our work in more detail as follows.

A. There Were Many Known Hurdles In Developing 5-Azacytidine As A Therapeutic.

9. In taking on the project of developing an oral formulation of 5-azacytidine, I was well aware of the known hurdles identified in the literature through decades of others trying to formulate 5-azacytidine.

10. 5-azacytidine is a nucleoside similar to the common nucleoside, cytidine. Ex.1001('628 patent), 2:37-62. 5-azacytidine has a nitrogen atom in place of a carbon atom present in cytidine, which is highlighted in the structure below (Ex.1001('628 patent), 2:48-62):



11. 5-azacytidine was well-known as a promising anti-tumor drug since the 1960s. *See, e.g.*, Ex.2012(Čihák), 2091, 2100 (noting the compound's “pronounced... cancerostatic effects). After administration of 5-azacytidine, cancer cells will incorporate the nucleoside into DNA and RNA. *Id.*, 3:9-27. 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...”
Id., 3:9-22.

12. Despite its promise as an anti-cancer drug, there were well-known problems of using 5-azacytidine as a therapeutic. In fact, Dr. Ladislav Hanka, who first purified 5-azacytidine, informed me of his difficulty in isolating 5-azacytidine due to its instability. *See also* Ex.2021(Lin), 1229 (recognizing that a “major problem encountered in the clinical formulation of 5-azacytidine is its chemical instability”).

13. One reason 5-azacytidine is unstable is that it breaks down in aqueous solutions via a process called hydrolysis. *See* Ex.1014(Chan), 807 (5-azacytidine’s “[i]nstab[ility] in aqueous solution” “ha[d] long been known.”); Ex.2003(Aparicio), 631 (concluding that “azacytidine... ha[s] not been dramatically successful [as a therapeutic], and pose[s] significant restrictions on dosing schedule adjustments because of [its] instability in aqueous solution and [its] side effects”).

14. Another reason 5-azacytidine is unstable is that an enzyme, cytidine deaminase, rapidly breaks down 5-azacytidine. *See* Ex.2009(Chabner), 2763, 2765 (noting that enzymatic degradation “may compromise the effectiveness of 5-azacytidine in treating human leukemia”).

15. Despite decades of research by several different entities, only one company, Pharmion, had successfully brought a 5-azacytidine product to market. In March 2004, Pharmion received FDA approval for the first 5-azacytidine formulation named Vidaza®, an injectable formulation for treating MDS. Ex.1007(Vidaza® Label 2004), 0008, 0023-0024; *see also* Ex.1008(Vidaza® Label 2007), 0008, 0011; Ex.2018(Kaminskas), 176.

16. The formulation and administration of Vidaza® were consistent with the known issues of 5-azacytidine as a treatment. Literature reported that 5-azacytidine needed to be “given immediately” intravenously after dissolution in water due to 5-azacytidine’s instability. Ex.2031(Weiss), 413-414, 418; *see* Ex.2090(Karon); Ex.2128(Von Hoff); Ex.2100(McCredie); Ex.2126(VoglerI); Ex.2127(VoglerII). Vidaza® is a lyophilized formulation that requires administration of the formulation shortly after reconstitution in water so a therapeutic pharmacokinetic profile is achieved before metabolism, hydrolysis, and degradation eliminate the drug. *See* Ex.1007-0008, -0023-0024(Vidaza® Label 2004); Ex.1008-0008, -0011(Vidaza® Label 2004).

B. We Began Work On An Oral Formulation of 5-Azacytidine Knowing The Significant Hurdles The Project Presented.

17. I started at Pharmion shortly after the approval of Vidaza® and was specifically tasked with developing an oral formulation of 5-azacytidine.

18. We were interested in developing an oral formulation because as an injectable formulation, Vidaza® presented challenges in administration and patient comfort. Administration of Vidaza® required patients to receive the injection for seven consecutive days every four weeks. Ex.1007-0022(Vidaza® Label 2004); Ex.1008-0011(Vidaza® Label 2007). Many patients reported injection-site reactions including discomfort. Ex.1007-0018-0021(Vidaza® Label 2004); Ex.1008-0010(Vidaza® Label 2007). In comparison, if it could be achieved an oral formulation could provide a more convenient treatment with less complications. *See* Ex.1001('628 patent), 3:50-54 (explaining that an oral administration “would be more desirable and convenient for patients and doctors,” “eliminat[e] injection-site reactions that may occur with SC [subcutaneous] administration,” and “permit[] improved patient compliance.”); *see also* Ex.2076(Curtiss), 575 (disclosing that oral dosage forms have potential benefits over injectable forms including “ease of administration, patient preference, and lower risk of complications”).

19. Despite the benefits that an oral formulation could provide, I was keenly aware that nobody had been successful in developing one and of the issues of hydrolysis and enzymatic degradation facing 5-azacytidine formulations. I knew of the work of several research groups that had attempted to develop an oral

formulation. None had been able to develop an oral formulation that was therapeutically effective.

20. For example, in the 1970s researchers reported that providing oral intubation of 5-azacytidine resulted in “much lower” 5-azacytidine blood levels compared to injectable formulations. Ex.2101(Neil), 463, 464. Researchers in 1985 reported that in administering 5-azacytidine orally to baboons, “only a fraction of the administered amount [wa]s available,” possibly because 5-azacytidine “is rapidly deaminated ... by cytidine deaminase, which is widely distributed in various tissues” including “the gastrointestinal mucosa....” Ex.2077(DeSimone), 285, 283-284; *see also* Ex.1031(Dover), Abstract, 528 (reporting no effect when oral 5-azacytidine was given alone, instead only seeing an increase in F reticulocyte production if given with tetrahydrouridine). Even when formulated to overcome deamination, such as by administering 5-azacytidine with a cytidine deaminase inhibitor, researchers determined that oral 5-azacytidine “was ineffective.” Ex.2079(Dunbar), 467. Along with the rest of the field, we understood that that “oral delivery of members of this class of compounds [of deoxycytidine and cytidine analogs] has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor tissue permeability.” Ex.2123(60/824,320), ¶[0007].

21. Given these well-documented issues and the failure of anyone to develop an oral formulation of 5-azacytidine, I had no expectation that we would be successful in our own efforts.

C. We Proposed An Enterically Coated Oral Formulation Of 5-Azacytidine To Overcome 5-Azacytidine's Known Issues

22. Starting around 2005, I began work to develop oral formulations of 5-azacytidine. I first conducted studies to determine in what part of the body 5-azacytidine would be best absorbed.

23. Specifically, I conducted a study using an *ex vivo* intestinal cell model, which suggested that 5-azacytidine is best absorbed through the colon. *See e.g.*, Ex.2123(60/824,320), ¶¶ [00105]-[00108]; Ex.2041(WO2008/028193), ¶¶[00120]-[00128]. Based on this and the well-documented issues with 5-azacytidine, I concluded that 5-azacytidine should be formulated “to avoid the chemical and enzymatic degradation occurring presystemically.” (Ex.1034(Stoltz).

24. I proposed that we develop a formulation of 5-azacytidine using an enteric coating so that the drug would release in the colon. I also believed that given the well-documented issues with 5-azacytidine degradation, an enterically-coated formulation might protect the drug from degradation in the stomach and upper gastrointestinal tract. Ex.2123(60/824,320), ¶¶[0022]-[0023], [00114]; Ex.2041(WO2008/028193), ¶¶[0024]-[0025], [00134]; Ex.1022, 2085-2094(Beach Decl.) (explaining that Pharmion “focused on [5-azacytidine formulations] that

were protected from the acidic environment of the stomach, *e.g.*, those requiring enteric coating[s],” consistent with the understanding in the field at the time); *see also* Ex.1001(’628 patent), 3:58-65. In other words, we believed that by delaying the release of 5-azacytidine beyond the stomach, *i.e.*, using an enteric coated formulation, we might improve oral bioavailability to target the colon through better tissue absorption and minimization of acid-dependent hydrolytic degradation. Ex.2123(60/824,320), ¶¶[0023]; *see also* ¶¶[00114].

25. We proposed and tested a number of enterically-coated formulations, and this work is described in U.S. Provisional Patent Application 60/824,320 and subsequent U.S. and international patent applications. See Ex.2123(60/824,320); Ex.2124(US2008/0057086), ¶¶[0132], [0137], [0174]; Ex.2041(WO2008/028193).

D. We Serendipitously Discovered That Non-Enteric Coated 5-Azacytidine Tablets Were Therapeutically Effective

26. Using an enterically-coated formulation of 5-azacytidine, we conducted a small-scale pilot study which showed absorption following oral administration.

27. Following up on these results, we performed additional tests using a second batch of enteric-coated tablets. *See* Ex.1001(’628 patent), Tables 4, 5, 7 (disclosing enteric-coated “Formulation 2”). Unlike our initial study, this second batch of enteric-coated tablets resulted in minimal absorption of 5-azacytidine. Repeating these tests with additional batches of enteric-coated 5-azacytidine

(“Formulation 4” and “Formulation 5”) also did not demonstrate significant absorption by patients. *See e.g.*, Ex.1050(61/157,875), Figs. 10-15, ¶¶[0039]-[0044], Tables 2-3, 5, ¶¶[00187], [00189]-[00193]; Ex.1051(’145 provisional), Tables 2-3; Ex.1001(’628 patent), Figs. 10-15, 9:6-25, Tables 3-5, 7, 73:1-74:16.

28. In problem-solving these inconsistent results, Dr. Lai and I looked back at the tablet compositions used in our first pilot study and discovered that the tablet formulation was manufactured incorrectly. Despite our instructions for the tablet to be enterically coated, we later learned that “Formulation 1” had a “leaky” enteric coating. Ex.1001(’628 patent), 64:19-21.

29. These results caused us to consider new ways of administering 5-azacytidine. Using what we learned from the pilot study, we hypothesized that 5-azacytidine could be administered in a therapeutically effective amount using a non-enteric coated tablet formulation. We therefore abandoned our research into enteric-coated tablets and took our research in a new direction. This new approach was contrary to our prior understanding, based on the decades of literature, that 5-azacytidine was chemically and enzymatically unstable such that it should not be released in the stomach or upper gastrointestinal tract.

30. We then engaged in extensive research to test our new hypothesis., We developed several different non-enteric coated tablets of 5-azacytidine “which did not undergo the enteric film-coating step” (*i.e.*, the non-enteric coated

“Formulation 3” and “Formulation 6”). Ex.1051(’145 provisional), ¶[0056], Figure 1. These non-enterically coated tablet formulations of 5-azacytidine are described in the ’628 patent. Ex.1001(’628 patent), Tables 3-5, 7, 64:29-50, Fig. 1.

31. Using the non-enterically coated tablet formulations of the ’628 patent, we demonstrated for the first time that non-enteric, “immediate release azacitidine formulations provide a superior percent exposure... than enteric-coated azacitidine formulations.” Ex.1001(’628 patent), 73:3-6; *see also id.*, 74:14-16; Ex.1051(’145 provisional), ¶[0070]. Specifically, we observed positive clinical activity in patients following administration of the non-enteric coated tablet formulation of 5-azacytidine. *See e.g.*, Ex.1001(’628 patent), 68:48-71:44; *see also* Ex.1050(’875 provisional), ¶[0174]-[0183]. Thus, contrary to the known chemical and enzymatic instability of 5-azacytidine, we made the surprising and unexpected “discovery that 5-azacytidine... [is] best absorbed and most efficaciously delivered if instantly released, upon oral administration, in the upper gastrointestinal tract, e.g., the stomach.” Ex.1051-0018(’145 provisional), ¶[0022].

32. In sum, and as described in the ’628 patent, we demonstrated for the first time that a ***non***-enteric coated ***oral*** tablet formulation of 5-azacytidine was therapeutically effective in treating AML or MDS. As we described in the ’628 patent, these non-enteric coated formulations “demonstrated bioavailability in patients” with “positive clinical activity [for] patients” and had superior exposure

compared to enterically coated formulations despite 5-azacytidine being released in the harsh gastric environment. *Id.*, 71:39-44, 73:1-6. We made this discovery serendipitously, running counter to over forty years of scientific research.

E. Non-Enteric Coated Tablets of 5-Azacytidine Displayed Unexpected Pharmacokinetic Results

33. I was surprised by the results of my team's fortuitous discovery that not only did a non-enterically coated tablet of 5-azacytidine provide a therapeutically effective amount, but it also provided a much higher amount than the analogous enterically coated formulations and provided strong efficacy as compared to a subcutaneous dose. Our studies showed that non-enteric coated tablets of 5-azacytidine demonstrated superior pharmacokinetic values as compared to enteric coated tablets.

34. For example, the patent describes that non-enteric coated tablets achieve **higher** maximum plasma concentration values. Figure 13, annotated and reproduced below, demonstrates that the non-enteric coated tablet, labeled "Formulation 3" or "F3," had a **higher** maximum plasma concentration than that of the enteric coated "Formulation 4" or "F4".

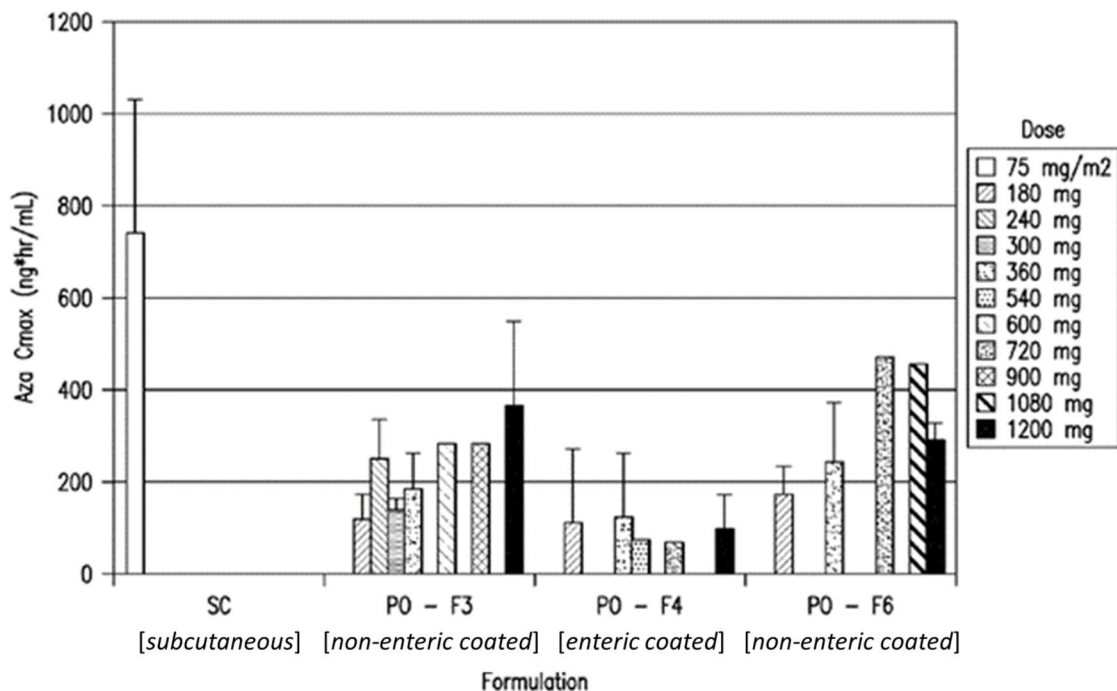


FIG. 13

Ex.1001('628 patent), Fig. 13; *see also id.*, Fig. 10, -0063, Table 7. Likewise, the '628 patent describes the non-enteric coated tablets provided **shorter** times to maximum plasma concentration (*id.*, Fig. 10, Fig. 16, 72:39-52, 72:44-58, 73:22-32, 74:18-23), **greater** area-under-the-curve values (*id.*, Fig. 12, 72:39-52, 72:44-58, 73:1-8, 74:4-16), and **larger** relative bioavailabilities (*id.*, Fig. 14, Fig. 15, 73:59-74:16) than corresponding enteric formulations.

35. In addition, our studies showed that the lower drug exposure of non-enterically coated oral 5-azacytidine provided surprisingly effective clinical results compared to higher levels achieved by traditional intravenous administration. In our studies, non-enteric tablets comprising 360 mg of 5-azacytidine or less achieved bioavailability of between 11% and 21% of that achieved with traditional

subcutaneously administered 5-azacytidine. *See* Ex.1001('628 patent), 73:64-74:3, Fig. 12, Fig. 14. Even though only a fraction of the 5-azacytidine was bioavailable, this low amount was surprisingly effective. For instance, non-enterically coated tablets containing either 240 mg or 300 mg of 5-azacytidine were provided to several patients diagnosed with MDS. *See* Ex.1001('628 patent), 66:50-67, Table 8. Not only did these non-enteric coated tablets “permit the delivery of azacitidine at lower doses over a more prolonged period of time,” but several of the patients exhibited notable improvements in their conditions following receipt of these lower doses released in the stomach. Ex.1001('628 patent), 71:9-18. I understand from discussions with Dr. Jay Backstrom and his team at the time that two of the patients receiving these non-enteric coated tablets exhibited *major* hematologic improvements, two patients exhibited *complete* morphological responses, and two patients exhibited extended *complete* marrow responses. Ex.1001('628 patent), Table 10. Thus, we surprisingly discovered oral 5-azacytidine’s ability to achieve positive clinical outcomes in patients despite a lower exposure to the drug than with subcutaneous doses. *See, e.g.*, Ex.1022, 2085-2094(Beach Decl.), 2093.

V. AVAILABILITY FOR CROSS-EXAMINATION

36. 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.

VI. RIGHT TO SUPPLEMENT

37. 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.

VII. JURAT

38. 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. Jeffrey B. Etter

Date: 11 Oct 2023

APPENDIX A

Jeffrey B. Etter, Ph.D.
Curriculum Vitae

SUMMARY:

Over 35 years of experience in the biotechnology/pharmaceutical industry in the areas of formulation development, analytical method development, manufacturing, and drug delivery of traditional and nuclear medicinal products. Extensive experience with project and personnel management, method and process validation, quality programs and regulatory requirements/submissions.

RESEARCH AND WORK EXPERIENCE:

ETTER CMC CONSULTING, LLC, BOULDER, CO

8/23 – Present Managing Member

Consulting to support drug substance and drug product development and manufacturing for clinical studies and commercial products

CLOVIS ONCOLOGY CORPORATION, BOULDER, CO

9/16 – 7/23 Senior Vice President Pharmaceutical Development

2/13 - 9/16 Vice President Pharmaceutical Development

3/10 – 2/13 Senior Director Pharmaceutical Development

7/09 – 2/10 Director of Pharmaceutical Development

Direction of process and analytical development at contract manufacturing and research organizations to produce both clinical and commercial drug substances. Direction of process, formulation, and analytical development at contract manufacturing and research organizations to produce oncology non-nuclear and nuclear drug products.

Responsibilities: Establishment and direction of strategic drug substance and drug product development and manufacturing programs. Identification and coordination of development, manufacturing, and testing facilities to execute those programs. Troubleshooting of manufacturing, formulation and analytical method issues for drug substance and drug product. Preparation and maintenance of division budgets. Coordination of Technical Operations, Validation, Manufacturing, Supply Chain Operations with Quality Assurance, Regulatory Affairs, Clinical Operations, and Commercial group activities. Review and approval of CMC sections for regulatory submissions. Interaction with Health Authorities on CMC related issues. Technical review of drug in-licensing opportunities.

PHARMION CORPORATION, BOULDER, CO

7/04 – 7/09 Director of Formulation Development

(As of March 2007, Pharmion was purchased by Celgene Corp)

Direction of formulation development, contract manufacturing, and research organizations relative to oncology drug products.

Responsibilities: Development of drug product formulation programs. Identification and coordination of testing facilities to execute those formulation programs. Troubleshooting of manufacturing, formulation and analytical method

issues for drug product. Compilation of drug product sections for regulatory submissions. Technical review of drug in-licensing opportunities.

ALLOS THERAPEUTICS, INC., WESTMINSTER, CO

9/02 – 7/04 Director of Drug Products

Direction of contract manufacturing and research organizations relative to oncology drug products.

Responsibilities: Simultaneous management of multiple contract drug product manufacturers. Establishment and monitoring of drug product stability studies. Trouble shooting formulation and analytical method issues for drug product. Compilation of drug product sections for regulatory submissions.

RXKINETIX INC., LOUISVILLE, CO

9/98 – 9/02 Vice President of Manufacturing

Direction of Manufacturing, Process Development, Formulation Development and Analytical Development for the production of innovative drug delivery products. Target drugs include proteins, peptides, genetic materials and small molecules.

Responsibilities: Develop research programs and establish standard operating procedures for formulation, analytical and production processes, coordination of collaborations with external clients, selection and management of contract manufacturing of clinical trial materials, submission of patent disclosures, and maintenance of division budgets and grants.

SOMATOGEN INC. (BAXTER HEALTHCARE), BOULDER, CO

2/97-9/98 Director of Analytical Development

(As of May 1998, Somatogen was purchased by Baxter Healthcare)

Management of all analytical development activities including Analytical Chemistry, Protein Chemistry, Immunoassay and Analytical Services laboratories in support of process validation and cGMP manufacturing operations.

Responsibilities: Direction of research, preparation of regulatory submissions, interaction and coordination with internal and external groups to ensure target production times, and development and maintenance of division budgets.

8/93-1/97 Staff Scientist (Grades II through Senior)

Direction of three research associates and of Analytical Services lab containing five technicians and one supervisor.

Responsibilities: Development, validation and technology transfer of analytical methods to be employed for in-process analysis, bulk product and final product release of recombinant human hemoglobin. Coordinated resources for process troubleshooting. Assistance in the preparation of regulatory submissions.

7/92-7/93 Manager Quality Control

Direction of a staff of two supervisors and twenty analysts covering chemical and microbiological analysis for manufacturing of recombinant human hemoglobin. Compliance with cGMP FDA regulations. Establishment of IQA program for process raw materials. Coordination with departmental heads for analytical services. Development and implementation of LIMS system.

1/91-6/92 Supervisor Quality Control
Development and validation of new analytical techniques. Compliance with cGMP FDA regulations. Assisted in the development of purification-isolation and final fill-finish strategies of product.

7/90-12/90 Process Development Scientist
Evaluation of physical characteristics of produced protein. Design and evaluation of drug formulations for improved stability.

BIOSTAR MEDICAL PRODUCTS INC., BOULDER, CO

6/88-6/90 Research Scientist
Research and development of novel techniques for covalent coupling biologically reactive proteins to continuous silicon surfaces for immunoassay production.

EDUCATION:

1987-1988 Postdoctoral Research Associate with Professor Barry M. Trost at Stanford University, Stanford, CA.

1982-1987 Ph.D. in Organic Chemistry with Professor Gary A. Molander at the University of Colorado, Boulder, CO.

1978-1982 A.B. in chemistry at Franklin and Marshall College, Lancaster, PA.

AWARDS AND HONORS:

1987-1988 National Institute of Health Postdoctoral Fellowship, Stanford University, Stanford, CA.

1985-1986 University of Colorado Fellowship, University of Colorado, Boulder, CO.

1983 John S. Meek Teaching Award, University of Colorado, Boulder, CO.

US PATENTS:

Oral Formulations of Cytidine Analogs and Methods of Use Thereof. Etter, J.B.; Lai, M.; Backstrom, J.T., *U.S. Patent Number 11,571,436, February 7, 2023*

Isotopologues of 5-Azacitidine. Traverse, J.F.; Leong, W.W.; Etter, J.B.; Lai, M.; Backstrom, J.T., *U.S. Patent Number 10,646,5033; May 12, 2020.*

Isotopologues of 5-Azacitidine. Traverse, J.F.; Leong, W.W.; Etter, J.B.; Lai, M.; Backstrom, J.T., *U.S. Patent Number 10,463,683; November 5, 2019.*

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High Dosage Strength Tablets of Rucaparib; Etter, J., *US Patent Number 10,130,636, November 20, 2018*

High Dosage Strength Tablets of Rucaparib; Etter, J., *US Patent Number 9,987,285, June 5, 2018*

Pharmaceutical Compositions of Cytidine Analogs and Method of Use Thereof. Tutino, A.; Lai, M.; Etter, J.B., *U.S. Patent Number 9,393,255, July 19, 2016*

Oral Formulations of Cytidine Analogs and Methods of Use Thereof. Etter, J.B.; Lai, M.; Backstrom, J.T., *U.S. Patent Number 8,846,628, September 30, 2014*

High-Concentration Protein Formulations and Method of Manufacture. Carpenter, J.F.; Etter, J.B.; Samaniego, A.C. *U.S. Patent Number 8,372,798, February 12, 2013*

Composition of Allosteric Hemoglobin Modifiers and Methods of Making the Same. Quick, A.; Santos, A.M.; Carvalho, A.J.G.G.; Johnson, D.G.; Etter, J.B.; Murray, C. *U.S. Patent Number 7,847,120, December 7, 2010.*

Flow-through Optical Assay Devices Providing Laminar Flow of Fluid Samples, and Methods of Construction Thereof. Drews, J.A.; Bogart, G.R.; Etter, J.B.; Steaffens, J.W.; Ostroff, R.M.; Crosby, M., *U.S. Patent Number 7,153,651 December 26, 2006.*

Particulate Drug-Containing Products and Method of Manufacture. Etter, J.B. *U.S. Patent Number 7,125,566, October 24, 2006.*

Device for Mass Transport Assisted Optical Assays. Drewes, J.A.; Bogart, G.R.; Etter, J.B.; Steafens, J.W.; Ostroff, R.M.; Crosby, M. *U.S. Patent Number 6,933,112, August 23, 2005.*

Composition for Delivery of Hematopoietic Growth Factor. Rosenthal, G.J.; Etter, J.B. *U.S. Patent Number 6,875,441, April 5, 2005.*

Particulate Insulin-Containing Products and Method of Manufacture. Etter, J.B. *U.S. Patent Number 6,761,909, July 13, 2004.*

Treatment of Mucositis. Rosenthal, G.J.; Etter, J.B.; Rodell, T.C.; Scahuer, W.H.; Samaniego, A. *U.S. Patent Number 6,685,917, February 3, 2004.*

Particulate Drug-Containing Products and Method of Manufacture. Etter, J.B. *U.S. Patent Number 6,669,960, December 30, 2003.*

Methods for Use of Delivery Composition for Expanding, Activating, Committing, or Mobilizing One of More Pluripotent, Self-Renewing and Committed Stem Cells. Talmadge, J.E.; Rosenthal, G.J.; Etter, J.B. *U.S. Patent Number 6,649,189 November 18, 2003.*

Methods for Detection of Gram Negative Bacteria. Bogart, G.R.; Modell, G.R.; Maul, D.M.; Etter, J.B.; Crosby, M. *U.S. Patent Number 5,869,272; February 9, 1999.*

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APPENDIX B

APPENDIX B - MATERIALS CONSIDERED

EXHIBITS

No.	Exhibit
1001	U.S. Patent No. 8,846,628 (“’628 patent”)
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”)
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”)
1022	Application File History for the ’628 Patent, U.S. App. No. 12/466,213 (“File History”)
1031	Dover, G.J., et al., <i>5-azacytidine Increases HbF Production and Reduces Anemia in Sickle Cell Disease: Dose-Response Analysis of Subcutaneous and Oral Dosage Regimens</i> , Blood, 66(3): 527-532 (Sep. 1985) (“Dover”)
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”)
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”)

No.	Exhibit
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”)
2012	Čihák, A & Šorm, F., <i>Biochemical Effects and Metabolic Transformations of 5-azacytidine in Escherichia coli</i> , 30 COLLECTION CZECHOSLOV. CHEM. COMMUN. 2091–2102 (1965) (“Čihák”)
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2031	Weiss, A., et al., <i>Phase I Study of 5-azacytidine</i> 56 CANCER CHEMOTHERAPY REP. 413–19 (1972) (“Weiss”)
2041	International Pat. Appl. Pub. No. WO2008/028193 (“WO2008/028193”)
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”)
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”)

No.	Exhibit
2100	McCredie, K., <i>Treatment of Acute Leukemia with 5-Azacytidine (NSC-102816)</i> , CANCER CHEMOTHERAPY REP. 57:319–23 (1973) (“McCredie”)
2101	Cancer Chemotherapy Reports, U.S. Dept. of Health, Edu., and Welfare (1975) (“Neil”)
2123	U.S. Provisional 60/824320 File History (“60/824,320”)
2124	U.S. Patent Application US 2008/0057086 (“US2008/0057086”)
2126	Vogler, W., et al., “Remission Induction in Refractory Myeloblastic Leukemia with Continuous Infusion of 5-Azacytidine” 16 PROCEEDINGS OF THE AM. ASS. FOR CANCER RESEARCH & AM. SOC. OF CLIN. ONCOLOGY (Mar. 1975) (“VoglerI”)
2127	Vogler, W., <i>5-Azacytidine (NSC 102816): A New Drug for the Treatment of Myeloblastic Leukemia</i> , 48 BLOOD 331–37 (1976) (“VoglerII”)
2128	Von Hoff, D., et al., <i>5-Azacytidine A New Anticancer Drug with Effectiveness in Acute Myelogenous Leukemia</i> , 85 ANNALS OF INTERNAL MEDICINE 237–45 (1976) (“VonHoff”)