IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Alexis Howerton et al.	
U.S. Patent No.:	12,115,166	Attorney Docket No.: 47291-0007PS1
Issue Date:	October 15, 2024	
Appl. Serial No.:	15/820,256	
Filing Date:	April 26, 2023	
Title:	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS	

DECLARATION OF DAVID E. BUGAY, PH.D.

I, David E. Bugay of Tavernier, FL, declare that:

I. INTRODUCTION

1. I have been retained by counsel for Petitioner Neurocrine Biosciences, Inc. to provide expert opinions in connection with a petition for *post grant* review of U.S. Patent No. 12,115,166 (the "'166 Patent"), assigned to Spruce Biosciences, Inc. ("Spruce"). Specifically, I have been asked to comment on issues related to stability as raised in Spruce's '166 Patent.

2. The opinions set forth below are based on my nearly 35 years of experience as an expert in analytical and physical-analytical characterization of pharmaceutical entities and on the results of analyses discussed in this report.

II. QUALIFICATIONS AND BACKGROUND INFORMATION

3. I am an expert in the areas of analytical chemistry, physical chemistry, physical analytical chemistry, and the characterization and analysis of active pharmaceutical ingredients ("API"), excipients, pharmaceutical intermediates and formulations, and pharmaceutical dosage forms. My expertise includes designing and executing stability studies that comply with regulatory requirements and interpreting the data acquired from said studies. Stability studies use high performance liquid chromatography and other appropriate analytical techniques to assess APIs and drug products under real-time and accelerated conditions. The data collected from such stability studies allows me to draw conclusions regarding

the chemical and/or physical stability of a given API and drug product, including recommending an appropriate shelf life.

4. I received my B.S. degree in Chemistry from Le Moyne College, in Syracuse, NY, in 1981. I then received my Ph.D. in Physical Chemistry at the University of Vermont in 1987.

5. After obtaining my Ph.D., I accepted a position as a Research Investigator in the Department of Analytical Research and Development at the Squibb Institute for Medical Research. Between 1990 and 1998, I held the positions of Senior Research Investigator I, Senior Research Investigator II, and then Principal Scientist in the Department of Analytical Research and Development at the Bristol-Myers Squibb Pharmaceutical Research Institute (BMSPRI).

6. From 1998 through May of 2008, I held senior positions within SSCI, Inc. which later became Aptuit, Inc. when Aptuit acquired SSCI in October 2006. SSCI/Aptuit is a contract research organization specializing in pharmaceutical development, including the characterization of various pharmaceutical entities (liquids, solids, gases, excipients, blends, formulated product, etc.). Initially, I was Vice President of Analytical Chemistry at SSCI and subsequently Senior Vice President of Analytical Chemistry. After Aptuit's purchase of SSCI, I was Managing Director of Aptuit Consulting. During these ten years, I managed and

led the Analytical Research Department, Analytical Resources Department, and Consulting Group and interacted with numerous pharmaceutical companies providing them with analytical services and consulting.

7. In June 2008, I founded my own consulting firm, PharmAnalysis, Inc., and in May 2009, I opened an accompanying laboratory, Triclinic Labs., Inc.

8. Triclinic Labs is a contract research company that provides a wide range of research and analytical services focusing on pharmaceutical entities. Services provided include solid form screening (including polymorphs, salts, co-crystals, and amorphous materials), solid form selection, crystallization method development, compendial testing, analytical method development, chemical and physical stability testing, solid-state characterization, problem solving, counterfeit analysis, containment analysis and identification, regulatory consulting, and other related consulting services.

9. Based on my experience, and in particular my experience relating to instrumental analysis, I have developed considerable expertise in analyzing and evaluating APIs, excipients, physical blends, intermediates isolated from manufacturing, formulated granules, and various types of drug products, including tablets, capsules, microspheres, suspensions, liquid formulations, and specialized formulations.

10. During my nearly 38 years working for BMSPRI, SSCI/Aptuit, and Triclinic Labs, I conducted analytical techniques on many different drug product formulations, API systems, formulation blends, intermediates, and excipients to understand the properties and stability of the API and finish dosage form.

11. While working at both SSCI/Aptuit and Triclinic Labs, I have assisted a large number of drug companies in analytical characterization, problem solving, stability testing, and regulatory issues relating to pharmaceutical drug development. In addition, I have assisted various pharmaceutical companies in legal matters relating to analytical, physical, and physical-analytical chemistry as a consultant or expert witness.

12. Throughout my career, I have been invited by numerous universities and institutions around the world to present lectures on various areas of my expertise in analytical, physical, and physical-analytical chemistry as applied to pharmaceutical development. I have authored or co-authored over 40 scientific publications, including seminar presentations, a textbook, book chapters, and papers. I am also a manuscript reviewer for several journals, including Pharmaceutical Research, Journal of Pharmaceutical Sciences, Applied Spectroscopy, Journal of Pharmaceutical and Biomedical Analysis, Organic Process Research and Development, and International Journal of Pharmaceuticals. In my capacity as a reviewer, I have refereed numerous manuscripts in the area of

pharmaceutical chemistry, including formulation design, analytical method development and validation, stability testing, characterization of APIs and formulations, formulation performance, and solid-state attributes of pharmaceutical entities.

13. From September 1998 to December 2009, I was an Adjunct Professor in the Department of Industrial and Physical Pharmacy at Purdue University in West Lafayette, Indiana. I taught a course to both undergraduate and graduate students entitled "Pharmaceutical Solids," which relates to the identification and characterization of solid-state forms of pharmaceutical compounds.

14. I have taught numerous other courses relating to the chemical and physical characterizations of pharmaceutical materials. Examples of such courses include the annual SSCI short course for pharmaceutical scientists entitled "Pharmaceutical Solids," an American Association of Pharmaceutical Scientists (AAPS) short course entitled "Characterization of Drug Substances—A Holistic Approach," and in-house courses to at least twenty different pharmaceutical companies located around the world. All of the courses presented include lectures on the use of various instrumental and chemical analysis techniques for the physical and chemical characterizations and stability of pharmaceutical materials.

15. In 2003, in recognition of my contributions to the field of pharmaceutical chemistry, I was elected as a Fellow of the American Association

of Pharmaceutical Scientists. Additionally, I was elected to the United States Pharmacopeia (USP) General Chapters Expert Committee for the term for 2005-2010. The General Chapters Expert Committee is responsible for reviewing, revising, generating, and updating chapters on analytical, physical, and physical-analytical technologies which are incorporated into the USP and utilized by the pharmaceutical community. During my term, the USP awarded the General Chapters Expert Committee the "USP Award for an Outstanding Contribution to the Standards-Setting Process." Additionally, I was appointed to the USP Spectroscopy Advisory Committee and the USP NMR Advisory Committee, which received a letter of merit for our contribution to the activities of USP. Finally, I was selected by USP to represent the United States at the World Health Organization's (WHO) meeting on counterfeit drugs and their impact on patient safety.

16. A copy of my curriculum vitae is provided (as Appendix A to this Declaration). This contains a list of my publications for at least the last ten years.

17. I am being compensated at my usual and customary rate of $1,050 per hour in addition to reimbursement of reasonable business expenses such as materials for experiments, instrument time, travel, and photocopying. My compensation is in no way based on the outcome of this matter and has not influenced my views in this matter.

III. ANALYSIS PERFORMED AND MATERIALS CONSIDERED

18. In forming my opinions set forth in this Declaration, I rely upon my knowledge and professional experience in the field of pharmaceutical chemistry, drug development, and drug characterization, as discussed above. In addition, I have considered in whole or in part the materials listed below:

Exhibit Number	Citation
1001	U.S. Patent No. 12,115,166 to Alexis Howerton, et al. ("the '166 patent").
1002	U.S. Prosecution History of the '166 Patent. Part 1, 1-624 Part 2, 625-1248 Part 3, 1249-1872 Part 4, 1873-2182 Part 5, 2183-2495 Part 6, 2496-3119
1032	Deore et al., "The Stages of Drug Discovery and Development Process," *Asian J. of Pharm. R. & D.* 7(6): 62-67 (2019) ("Deore").
1038	Yamaguchi et al., "Approval success rates of drug candidates based on target, action, modality, application, and their combinations," *Clin. Transl. Sci.* 14:1113-22 (2021) ("Yamaguchi").
1050	"Guidance for Industry, Q1A(R2) Stability Testing of New Drug Substances and Products," U.S. Department of Health and Human Services, Food and Drug Administration (November 2003).
1051	"Guidance for Industry, Q1E Evaluation of Stability Data," U.S. Department of Health and Human Services, Food and Drug Administration (June 2004).

IV. INTERPRETATION OF THE '166 PATENT CLAIMS AT ISSUE

19. I understand that, for purposes of my analysis in this *post grant* review proceeding, the terms appearing in the '166 Patent claims should be interpreted according their ordinary and customary meaning as understood by a person of ordinary skill in this art ("POSA"), as discussed in Section VI, in view of the patent's disclosure and prosecution history. In that regard, I understand that the best indicator of a claim term's meaning is its usage in the context of the patent specification as understood by a POSA. I further understand that the words of the claims should be given their plain meaning unless that meaning is inconsistent with the patent specification or the patent's history of examination before the Patent Office. I also understand that the words of the claims should be interpreted as they would have been interpreted by a POSA at the time the invention was made (not today). Because I do not know at what date the invention as claimed was made, I have used the earliest priority date of U.S. Patent No. 12,115,166 as the point in time for claim interpretation purposes. That date is August 14, 2017, the date the first provisional application in this patent family was filed. I currently have not been asked to provide opinions on the interpretation of particular terms and phrases of the '166 Patent but reserve the right to do so if asked or in response to any arguments or opinions set forth by Spruce and its expert(s).

V. LEGAL STANDARDS

A. Written Description

20. I understand that the specification must contain a "written description" of the claimed invention that allows a person of ordinary skill in the art to recognize that the inventor invented what is claimed. I understand that the test for written description is whether the disclosure in the specification reasonably conveys to a POSA that the inventor had possession of the full scope of the claimed invention as of the filing date. I understand that the written description requirement is applied in the context of the state of knowledge in the art at the time the patent application was filed.

21. The level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. I understand that factors used to evaluate the sufficiency of a disclosure include: 1) the existing knowledge in the particular field; 2) the extent and content of the prior art; 3) the maturity of the science or technology; and 4) the predictability of the claimed method or invention.

22. I understand that when a claim recites a genus of compounds using functional language to define a claimed result, the specification must disclose either a representative number of compounds falling within the scope of the genus

that achieve the claimed result, or structural features common to the members of the family that achieve the claimed result, so that a POSA can visualize or recognize the members of the family.

VI. PERSON OF ORDINARY SKILL IN THE ART

23. I understand the POSA as relevant to the '166 Patent has already been defined by Neurocrine's experts, including by Dr. Maya Lodish. I agree with this definition, which is reproduced below.

24. A POSA would have a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, and knowledge of the treatment regimens employed to treat such disorders. The POSA would also have at least three years of experience conducting research concerning endocrine disorders, including CAH and other adrenal disorders. A POSA may have also worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem, including analytical chemistry and pharmaceutical formulation.

25. I consider myself as someone who the POSA would have consulted with, at least as of the earliest relevant timeframe, 2017.

VII. TECHNOLOGY BACKGROUND

A. Drug Discovery Process

26. Discovery of new drug compounds for therapeutic uses is a long, expensive, and labor-intensive process. Typically, from the drug discovery phase to FDA approval, it may take 12-15 years of work and hundreds of millions of dollars of investment. *See* EX1032, 62. The drug development process can be thought of in several steps—discovery and development, preclinical research, clinical research, FDA review, and FDA post-market safety monitoring. *Id*., 63-65.

27. The drug discovery phase generally entails scientists identifying a target for a drug to act on and then screening different molecular compounds to find the best compound that provides beneficial effects against the target. This process entails trial and error. At this stage, tens of thousands of compounds are evaluated in laboratory tests over the course of several years before only a handful are advanced to preclinical testing and development. *Id*., 63-65; *see also* EX1038, 1114.

28. Once candidates are advanced to the preclinical testing and development stage, their properties are thoroughly evaluated to understand potential efficacy and safety risks before use in any human clinical trial. Preclinical development testing may include experiments to understand how the

drug candidates are absorbed, distributed, metabolized, or excreted, their mechanism of action, potential efficacy, and stability, the best dosages, preferred routes of administration (e.g., oral versus injectable), potential side effects (toxicity), and whether such candidates interact with other drugs. EX1032, 64-65.

29. Once a lead candidate is further assessed and characterized through the preclinical development stage, that candidate is evaluated in multiple clinical studies in humans to evaluate safety and efficacy. Most clinical programs will evaluate drug candidates in phase 1, phase 2, and phase 3 trials that will run over the course of several years. The likelihood of drug candidates successfully proceeding through phase 1 all the way through phase 3 clinical trials and marketing approval is low—10-20%. EX1038, 1114.

B. Overview of Stability for Drug Products

30. The Food and Drug Administration (FDA) is the public health agency charged with, among other things, approving new or generic drugs to enter the market and monitoring the safety and efficacy of existing drugs. When approving a new drug or a generic version of an existing drug, the FDA generally does not conduct its own testing. Rather, the FDA analyzes the testing performed by the manufacturer to determine if the newly submitted drug is safe and effective for human use.

31. The FDA provides guidelines for how manufacturers can perform drug testing and what data may be included in a new or abbreviated drug application. For example, the FDA provides guidelines on how a manufacturer can perform stability testing and what stability data is required for approval.

32. The FDA has adopted guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on, among other things, stability testing for new drugs. *See* EX1050; EX1051.

33. The purpose of stability testing is to show the stability characteristics of a drug substance (also known as the API) and/or drug product over various time periods and once exposed to various environmental factors, like temperature, humidity, and/or light. EX1050, 1.3. Stability testing provides a stability profile eventually leading to the establishment of an estimated shelf life and recommended storage conditions for a drug. *Id.* Under FDA guidelines, stability studies should test any attribute of the drug that is susceptible to change or likely to influence qualify, safety, or efficacy. *Id.,* 2.2.5. Thus, the specific stability tests that are performed for a given drug will vary based on, among other things, the physical and chemical properties of the drug. *Id.* Stability testing on both the drug substance (unformulated) and drug product (in final dosage form) is required in new and abbreviated drug applications.

34. The FDA provides specific guidance on how the API and final dosage form (drug product) should be tested based on the storage conditions and shelf life proposed by the drug's manufacturer. For example, an aqueous-based product in a semipermeable container should be tested for water loss, and a product to be stored in a refrigerator should be tested at refrigerator temperatures. *Id*., 2.2.7.3, 2.2.7.4. The proposed shelf life and length of a stability study should be sufficient to cover storage, shipment, and subsequent use. *Id*., 2.2.7.

35. Generally, for a drug that is to be stored at room temperature, stability testing is performed under the following conditions. *See id*., 2.2.7.1.

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

36. For a drug that is to be stored in refrigeration, stability testing is performed under the following conditions. *See id*., 2.2.7.4.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

VIII. U.S. PATENT NO. 12,115,166

37. The ’166 Patent is generally directed to a pharmaceutical composition comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(l-ethylpropyl)-2,5-dimethylpyrazolo(l ,5-a)pyrimidine (“Compound 1”) and methods of using the same for the treatment of congenital adrenal hyperplasia (CAH). EX1001, Abstract. I understand that Compound 1 as described in the ’166 Patent is the compound known as tildacerfont.

38. The ’166 Patent contains only 1 independent claim. Claim 1, reproduced below for ease of reference, recites:

> [a] method for treating congenital adrenal hyperplasia (CAH) in a human comprising:
>
> administering to said human a therapeutically-effective amount of a CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof,
>
> wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and administering to said human a second dose of a glucocorticoid,
>
> wherein said second dose of a glucocorticoid is reduced compared to said first dose of a glucocorticoid,
>
> wherein an androstenedione (A4) level in said human is reduced from baseline, or
>
> wherein an adrenocorticotropic hormone (ACTH) level in said human is reduced from baseline, or
>
> wherein a 17-hydroxyprogesterone (17-OHP) level in said human is reduced from baseline,

> wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein said CRF1 receptor antagonist is stable for storage for a minimum of six months.

39. As I discuss above, my opinions relate to chemistry, manufacturing, and controls (CMC) aspects of Spruce's alleged invention claimed in the '166 Patent. Thus, I also have reproduced below for ease of reference, Claim 21 which recites:

> [t]he method of claim 1, wherein said CRF1 receptor antagonist is stable between about 25℃ and about 40 ℃.

40. The specification of the '166 Patent provides certain limited teachings regarding stability. The specification describes "stable" as "pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period." EX1001, 25:21-26. The specification goes on to describe the allowed amounts of impurities for embodiments of pharmaceutical compositions containing Compound 1. For example, the specification states "[i]n some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, 1.5% w/w, about 1% w/w or about 0.5% w/w total impurities or related substances." *Id*., 25:29-34.

41. The specification describes the stability at refrigerated, ambient, and accelerated conditions. For example, "[a]t refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months." *Id*., 25:46-51. The '166 Patent further specifies that for some embodiments, "refrigerated conditions" is 5±5°C. *Id*., 25:51-53.

42. Similarly, the '166 Patent describes the stability of pharmaceutical compositions of Compound 1 at accelerated conditions. For example, the specification states "[a]t accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 months." *Id.*, 26:15-21. "Accelerated conditions" include temperatures that are at or above ambient level, ranging from 20°C to 60°C, and relative humidity that are at or above ambient levels, ranging from 45% RH to 80% RH. *Id*., 26:15-33.

43. The specification further describes "[i]n some embodiments the pharmaceutical compositions are stable at about 5±5°C to about 25±5°C for at least 12 months." EX1001, 26:38-40; *see also id.*, 26:40-48.

44. The specification provides a summary of limited stability data in Example 2. *See id*., 34:58-36:57. Table 1 (column 35) provides a summary of the stability of three lots of Compound 1 neat-filled into size 0 capsules with no added excipients at different strengths—1 mg, 5 mg, and 50 mg—along with three lots of capsules containing 200 mg of Compound 1 in HDPE bottles, which I have reproduced below:

TABLE 1

Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25° C./60% RH	6 months
			40° C./75% RH	6 months
#2	5-mg	PVC-based blister pack	25° C./60% RH	6 months
			40° C./75% RH	6 months
#3	50-mg	PVC-based blister pack	25° C./60% RH	6 months
			40° C./75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25° C./60% RH	1 month
			40° C./75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25° C./60% RH	6 months
			40° C./75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25° C./60% RH	6 months
			40° C./75% RH	6 months

CCS = container closure system;
CRC = child-resistant closure;
DoM = date of manufacture;
HDPE = high density polyethylene;
PVC = polyvinyl chloride

45. The ’166 Patent concludes after Table 1 that “[u]nder long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.” EX1001, 35:1-4.

46. Table 1 is accompanied by Tables 2-4, which also discuss stability, however, the disclosures in Tables 2-4 are limited to stability protocols. Tables 3-4

(columns 35-36), for example, show the stability protocols for 200-mg capsules in 30 mL HDPE (high density polyethylene) bottles.

IX. OPINION – THE '166 PATENT DOES NOT PROVIDE SUPPORT FOR THE CLAIMED STABILITY LIMITATION

47. I have reviewed the disclosures of the '166 Patent in view of claims 1-10 and 12-21 (the "Challenged Claims"). In my opinion, the required stability limitation of Claim 1 (and its dependent claims)—"wherein said CRF1 receptor antagonist is stable for storage for a minimum of six months"—is not supported by the specification. A POSA viewing the specification would understand that it describes the stability of only one CRF1 receptor antagonist—Compound 1 (tildacerfont). As I discuss in further detail below, a POSA would not understand Spruce to have sufficiently described the stability for the members of the claimed large genus of CRF1 receptor antagonists.

48. A POSA reading the specification would immediately understand that the "present invention" is pharmaceutical compositions and methods using 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(l-ethylpropyl)-2,5-dimethylpyrazolo(l ,5-a)pyrimidine, which is tildacerfont. *See* EX1001, Abstract. And while the term "pharmaceutical compositions" is used throughout the specification, a POSA would have no question that it means pharmaceutical compositions of Compound 1 (tildacerfont). For example, under the heading "Pharmaceutical Compositions," the specification states "[d]isclosed herein is a pharmaceutical composition

comprising Compound 1, a pharmaceutically acceptable salt, and/or a solvate thereof." EX1001, 15:1-4.

49. With respect to stability, the specification states that "[s]table as used herein refers to pharmaceutical compositions having about 95% or greater **of the initial Compound 1 amount** and about 5% w/w or less total impurities or related substances at the end of the a given storage period." *Id*., 25:22-26 (emphasis added). The specification goes on to make clear that the "percentage of impurities is calculated from the amount of impurities **relative to the amount of Compound 1**." *Id*. 25:26-28 (emphasis added). With that framework in mind, a POSA would understand that any stability disclosures in the '166 Patent are limited to only tildacerfont. These stability disclosures include discussion of stability in various storage conditions, "including refrigerated, ambient, and accelerated conditions," (*id.*, 25:19-22) as well as lists of temperature and humidity parameters for those conditions (*id.*, 25:46-26:15; 26:22-48). They also include discussion of the amount of impurities allowed for the pharmaceutical compositions comprising tildacerfont (*id.*, 25:29-45) and stability storage duration (*id*., 25:46-51, 26:15-21).

50. There is only one example in the specification of the '166 Patent regarding stability—Example 2. Example 2 provides a summary of a stability study conducted on tildacerfont that was neat-filled in capsules and then blister packaged or bottled. *See* EX1001, 34:58-67. A summary of stability conditions

for these neat-filled capsules is found in Table 1. The specification states with respect to the tildacerfont stability testing that "[u]nder long term and accelerated condition, no significant trend was observed in three lots for any of the attributes evaluated throughout the course of the stability study." *Id*., 35:1-4. Example 2 also includes Tables 2-4, which set forth stability protocols, but do not include any quantitative stability data for tildacerfont, nor any other CRF1 receptor antagonist. *See id*., 35:31-36:44. Based on this testing, the specification concludes that "[t]he supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study)." *Id*., 36:45-47.

51. In my opinion, a POSA reading the stability disclosures in the '166 Patent would understand they are limited to tildacerfont alone. There is no stability testing or data for any other CRF1 receptor antagonist nor would a POSA be able to predict the stability of any other CRF1 receptor antagonist in the sweeping genus of the Challenged Claims without testing for it. For example, a POSA would understand that stability can be affected by the dosage form of a pharmaceutical. *See supra,* § VII.B. But the specification only discloses stability information for Compound 1 (tildacerfont). *See* EX1001, Example 2. Spruce's own representations to the patent office are in agreement. I understand that in order to convince the patent office to allow the Challenged Claims, Spruce argued to the Examiner that the claimed dosages of Compound 1 tested in Example 2 were

special having "an unexpected benefit of being more stable for shelf storage." EX1002, 2501. A POSA would understand from Spruce's representations that Compound 1 (tildacerfont), purportedly, has unique stability properties and would not be able to extrapolate such properties to other members of the claimed CRF1 receptor antagonist genus.

52. Further, a POSA reading the Challenged Claims would understand that they are broad enough to encompass any type of dosage form for any one CRF1 receptor antagonist in the sweeping claimed genus. As I discuss above, there are different criteria for determining stability for different pharmaceutical dosage forms. *See supra,* § VII.B. Yet, the specification provides no data or other disclosures, for the stability of any CRF1 receptor antagonists other than Compound 1 (tildacerfont). A POSA would find this lack of disclosure further compounds the deficiency of the specification in demonstrating the stability of any member of the claimed CFR1 receptor antagonist genus.

53. In my opinion, the Challenged Claims of the '166 Patent are not supported by the specification and lack the requisite written description for the stability limitation.

X. RESERVATION OF RIGHTS

54. This declaration sets forth my opinions to date. But my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

55. I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare 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 the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 10, 2025 By: _____

David E. Bugay

APPENDIX A

DAVID E. BUGAY

EDUCATION

Ph.D., Physical Chemistry, May 1987
University of Vermont, Burlington, VT 05405

Research Advisors: Dr. Willem R. Leenstra and Dr. C. Hackett Bushweller
Thesis Subject: Triplet state infrared vibrational studies involving polycyclic aromatic hydrocarbons, combined with the determination of extinction coefficients of cyclohexyl halides through equilibrium measurements by FTIR and FTNMR.

B.S., Chemistry, May 1981
Le Moyne College, Syracuse, NY 13214

EMPLOYMENT EXPERIENCE

Chief Scientific Officer/Consultant, **Triclinic Labs, Inc.**, Lafayette, IN, March 2009 to present

President/*Consultant*, **PharmAnalysis, Inc.**, West Lafayette, IN, June 2008 to present.

Affiliate Consultant, **Aptuit Consulting, Inc.**, West Lafayette, IN, June 2008 to March 2013.

Managing Director, **Aptuit Consulting, Inc.**, West Lafayette, IN, October 2006 to May, 2008.

Senior Vice President of Analytical Chemistry, **SSCI, Inc.**, West Lafayette, IN, April 2005 to October 2006.

Vice President of Analytical Chemistry, **SSCI, Inc.**, West Lafayette, IN, March 1998 to April 2005.

Adjunct Professor, Department of Industrial and Physical Pharmacy, **Purdue University**, West Lafayette, IN 47905, September 1998 to December 2009.

Principal Scientist, Analytical Research & Development, **The Bristol-Myers Squibb Pharmaceutical Research Institute**, a division of Bristol-Myers Squibb Corporation, New Brunswick, NJ 08903-0191, August 1997 to February 1998.

Senior Research Investigator II, Analytical Research & Development, **The Bristol-Myers Squibb Pharmaceutical Research Institute**, a division of Bristol-Myers Squibb Corporation, New Brunswick, NJ 08903-0191, August 1994 to August 1997.

Senior Research Investigator I, Analytical Research & Development, **The Bristol-Myers Squibb Pharmaceutical Research Institute**, a division of Bristol-Myers Squibb Corporation, New Brunswick, NJ 08903-0191, April 1990 to August 1994.

Research Investigator, Analytical Research & Development, **The Squibb Institute for Medical Research**, a division of E.R. Squibb & Sons Pharmaceutical, New Brunswick, NJ 08903, May 1987 to April 1990.

AWARDS

Fellowship - American Association of Pharmaceutical Scientists, October 2003.

US PATENTS

I. Ivanisevic, S. Bates, D.E. Bugay, B.C. Stahly, and D.R. Hallenbeck, *System and Method for Matching Diffraction Patterns*, US Patent 7,372,941, issued May 13, 2008.

APPOINTMENTS United States Pharmacopeia (USP), 2005-2010, General Chapters Expert Committee.
United States Pharmacopeia (USP), 2008-present, NMR Advisory Panel.
United States Pharmacopeia (USP), 2008-present, Spectroscopy Advisory Panel.
United States Pharmacopeia (USP) representative to the World Health Organization IMPACT Meeting: Counterfeit Pharmaceuticals and Medical Products, February 2008.

MANUSCRIPT REVIEWER *Pharmaceutical Research, Journal of Pharmaceutical Sciences, Pharmaceutical Review, Journal of Pharmaceutical and Biomedical Analysis, International Journal of Pharmaceutics, Organic Process Research and Development, Applied Spectroscopy, and Journal of Raman Spectroscopy*

RESEARCH EXPERIENCE

Vibrational Spectroscopy (IR, Near-IR, Raman, Low-Frequency Raman, and Terahertz Pulsed): Development of multi-component, quantitative assays for pharmaceutical compounds. Solid-state investigations utilized diffuse reflectance, ATR, IR and NIR imaging, Raman mapping, TG-IR, bulk analysis, and IR/Raman microspectroscopy methods, whereas solution phase studies involved CIRCLE™ cell, fiber optic, and neat sampling techniques. Quantitative method development under ICH conditions for API, intermediates, physical blends, and drug product materials. Experience with the utilization of mapping/imaging techniques for the characterization of pharmaceutical drug products. These vibrational studies have been combined with AFM, μTA, ToF-SIMS, EDS, and micro-XRPD studies for the complete physical characterization of dosage forms.

Nuclear Magnetic Resonance Spectroscopy (Solution- and Solid-State NMR): Multinuclear (^{1}H, ^{13}C, ^{31}P, ^{15}N, ^{27}Al, ^{29}Si, ^{35}Cl etc.) characterization of pharmaceutical materials (bulk and dosage form) by various 1- and 2-D pulse sequences and variable temperature techniques. Assays have been developed for the quantitation of impurities in solution, polymorphic forms in solid API and dosage forms. Multinuclear solution-phase studies for structure elucidation, quantitative analysis, and problem solving.

Thermal Analysis (DSC, MDSC, TGA, TG-IR, μTA): Thermal analysis techniques have been developed and utilized to study polymorphism, amorphous materials, and drug-excipient interactions. These studies have been performed at the qualitative and quantitative levels with API and drug product. Experience with the use of microthermal analysis techniques utilizing the AFM.

Diffraction (single crystal and powder): Extensive experience with the use of x-ray and electron diffraction for the study of pharmaceutical solids (single crystals, powder, and drug product samples). Utilization of ambient, VT, and VRH conditions to study solid-state forms of materials (crystalline, semi-crystalline, amorphous). Development of quantitative methods for phase purity at the API and drug product level. Experience in the interpretation of single crystal diffraction data, structure solving, and calculation of powder patterns from structure elucidation. Utilization of micro-diffraction techniques to map the physical form of pharmaceutical solids in drug products. Computerized tomography (CT) used to characterize medical devices.

Microscopy (ESEM, SEM, AFM, Optical, Vibrational, fluorescence, EDS, ToF-SIMS): Investigative studies on particle morphology, drug product composition, contaminant analysis, and elemental analysis through the combined use of SEM, ESEM, AFM, optical, fluorescence, TOF-SIMS, and energy dispersive X-ray microscopy.

General Techniques (UV/VIS, Dissolution, Disintegration, USP Testing, PSA, Moisture Sorption/Desorption, HPLC, GC, Micromeritics, Mass Spectrometry): Significant experience in general testing such as pH, LOD, KF, particle size analysis, surface area, dissolution, disintegration, UV/VIS, elemental analysis, HPLC, GC, LC-MS, MS, and other USP testing procedures. Use of moisture and organic vapor sorption/desorption studies for the qualitative and quantitative characterization of pharmaceutical solids.

Multivariate Analysis: During the course of studying pharmaceutical solids, significant experience has been gained in the use of uni- and multivariate techniques for the processing of chemical data. Pattern recognition techniques such as hierarchical cluster analysis and principal component analysis have been used. Quantitative methods have been developed utilizing direct and inverse techniques such as classical least squares, P- and K-matrix, PCR, and extensive use of PLS methodology.

Scientific Computing: Extensive experience with personnel computer systems and software: Word, Excel, PowerPoint, etc. Knowledge of various empirical and semi-empirical quantum mechanical computational methods: MM2, MNDO, QCFF, MINDO, AMPAC, and Cerius^2 programs. Remote, off-line data processing for spectroscopy utilizing GRAMS/AI, ISYS, Unscrambler, Spartan, and Mercury.

PROFESSIONAL ORGANIZATIONS

American Association of Pharmaceutical Scientists (APQ and PT Sections)
American Chemical Society, Physical Chemistry Division
Society of Applied Spectroscopy, Near IR Council Member

Presentation and Publication Listing

INVITED SEMINARS

INAME (Argentinean Regulatory Authority) Symposium, *"Raw Material ID: Pharmaceutical Compliance,"* Buenos Aires, Argentina, April 28, 2011.

United States Pharmacopeia Annual Scientific Meeting 2009, Advisory Panel Symposium, *"Adulteration and Contamination: Technologies of the Future: Overview of Instrumentation,"* Toronto, ON, Canada, September 22, 2009.

Ahura Scientific TruScan Workshop and Advisory Board, *"Raman Spectroscopy: An Evolving Technology for Pharma,"* Boston, MA, October 23, 2008 & Windsor, UK, June 5, 2009.

United States Pharmacopeia Annual Scientific Meeting 2008, Advisory Panel Symposium, *"Spectral Libraries: Current Status, Usage, and How They May be Incorporated into the USP,"* Kansas City, MO, September 23, 2008.

Washington, D.C. Bar Association Meeting, *"Where Pharmaceutical Science and Patent Law Battle: Polymorphs and the Solid-State, Case Studies"*, Washington, D.C., March 20, 2007.

European Patent and Trademark Office, *"Analytical Techniques Used for the Physical Characterization of Pharmaceutical Solids"*, Munich, Germany, December 1, 2006.

United States Patent and Trademark Office, *"Analytical Techniques Used for the Physical Characterization of Pharmaceutical Solids"*, Alexandria, VA, October 11, 2006.

United States Pharmacopeia Annual Scientific Meeting 2005, Session II, Track I: Analytical Validation and Verification of Compendial Methods, "*Validation of Spectroscopic Test Methods"*, San Diego, CA, September 27-30, 2005.

Tenth Arden House European Conference in association with AAPS and RPSGB, Materials Science - Characterization of Pharmaceutical Materials for Candidate Selection, Formulation Development, Good Process Outcomes, and Regulatory Approval, *"Advances in Spectroscopic Methods for Solid-State Characterization"*, London, UK, March 21-23, 2005.
Nicolet Instruments Research Symposium, *"Vibrational Spectroscopy in*

Pharmaceutical Development", Montreal, Quebec, February 3, 2005.

American Association of Pharmaceutical Scientists 40th Annual Pharmaceutical Technologies Conference at Arden House, Pharmaceutical Materials Science - From Drug Substance to Drug Product, *"Spectroscopic Techniques for the Characterization of Pharmaceutical Solids"*, Harriman, NY, January 23-28, 2005.

2004 American Association of Pharmaceutical Scientists Meeting and Exposition,Roundtable Session: Validation of Non-Chromatographic Methods, *"Implementation of ICH Validation Guidelines for the Validation of Solid Form Quantitative Assays"*, Baltimore, MD, November 7-11, 2004.

NATO International School of Crystallography, 35th Course: Diversity Amidst Similarity: A Multidisciplinary Approach to Polymorphs, Solvates, and Phase Relationships, Lecture: *"Polymorphism and Raman Spectroscopy"*, Erice, Sicily, Italy, June 9-20, 2004.

NATO International School of Crystallography, 35th Course: Diversity Amidst Similarity: A Multidisciplinary Approach to Polymorphs, Solvates, and Phase Relationships, Lecture: *"Quantitative Analysis of Polymorphic Mixtures"*, Erice, Sicily, Italy, June 9-20, 2004.

NATO International School of Crystallography, 35th Course: Diversity Amidst Similarity: A Multidisciplinary Approach to Polymorphs, Solvates, and Phase Relationships, Workshop: *"Developing Methods for the Quantitative Analysis of Polymorphic Mixtures"*, Erice, Sicily, Italy, June 9-20, 2004.

American Chemical Society ProSpectives Conference Series, *Polymorphism in Crystals: Fundamentals, Prediction, and Industrial Practice*, *"Quantitative Phase Analysis: Approaches, Limitations, and New Directions"*, Tampa, FL, February 23-26, 2003.

Nicolet Instruments Research Symposium, *"Characterization of Pharmaceuticals by IR and Raman Spectroscopy"*, Vancouver, BC/San Diego, CA; San Francisco, CA; Research Triangle Park, NC, November 21, 2002/January 16, 23, and 30, 2003.

Seventeenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *Sunrise Pharmacy School, Techniques in Solid-State Characterization, Spectroscopic Methods for Characterization of Drug Substances"*, Toronto, ON, Canada, November 13, 2002.

Forty-Second Annual Conference on Pharmaceutical Analysis – Land O'Lakes Conference, *"Drug Product Analysis by Raman Spectroscopy"*, Devil's Head Lodge, Merrimac, WI, July 29-August 2, 2002.

AAPS Workshop on Chemical and Physical Form Selection of Drug Candidates: Principles, Considerations and Case Studies, *"Analytical Techniques Used in the Solid-State Characterization of Pharmaceuticals Salts and Polymorphs"*, Arlington, VA, April 25-26, 2002.

Nicolet Instruments Research Symposium, *"Drug Product Analysis by Raman Spectroscopy"*, Research Triangle Park, NC, December 13, 2001.

Fortieth Eastern Analytical Symposium and Exposition, *Symposium: Vibrational Spectroscopy in the Pharmaceutical Industry: "Phase Purity Analysis of a Drug Substance by Raman Spectroscopy"*, Atlantic City, NJ, October, 2001.
Sixteenth Annual American Association of Pharmaceutical Scientists Meeting and

Exposition, *Symposium: New Analytical Technology Applications for In Situ Analysis of Dosage Forms: "Drug Product Analysis Using Raman Spectroscopy"*, Denver, CO, October 23, 2001.

Pharmaceutical Spectroscopy Symposium, *Workshop #2: Utilizing Molecular Spectroscopy for Drug Development*, Philadelphia, PA, June 21-22, 2001.

Pharmaceutical Congress of the Americas, *Importance of Solid-State Behavior in the Development of Pharmaceutical Dosage Forms Short Course, "Practical Issues/Characterization Methods: Spectroscopic Techniques"*, and *"Practical Issues/Characterization Methods: Regulatory Considerations"*, Orlando, FL, March 25, 2001.

Nicolet Instruments Research Symposium, *"IR and Raman of Pharmaceutics: Quantitative Assays and Mapping"*, San Francisco, CA/Princeton, NJ, January 18, January 25, 2001.

Thirty-Ninth Annual Eastern Analytical Symposium and Exposition, New York Microscopical Society's Ernst Abbe Award to Maria Kuhnert-Brändstatter, *"Polymorphism Analysis: From Optical Microscopy to Molecular Spectroscopy,"* Atlantic City, NY, November 2, 2000.

Second International Symposium on Polymorphism and Crystallization, Chemical Development Issues, *"Current Analytical/Regulatory Issues Concerning Polymorphism and Crystallization,"* Chester, Cheshire, United Kingdom, October 16-18, 2000.

Nicolet Instruments Research Symposium, *"Solid-State Pharmaceutical Analysis by Vibrational Spectroscopy"*, Princeton, NJ/San Francisco, CA, November 30, February 8, 1999-2000.

Fourteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *Roundtable Discussion Moderator and Speaker: "Molecular Spectroscopy: Current Status in the Pharmaceutical Industry",* New Orleans, November 14-18, 1999.

Aspects of Polymorphism and Crystallization Symposium, *"Quantitative and Regulatory Aspects of Polymorphism"*, Hinkley, Leicestershire, United Kingdom, June 23-25, 1999.

Tenth International Symposium on Pharmaceutical and Biomedical Analysis, *Short Course: Physical Characterization of Pharmaceutical Solids*, co-presented with Dr. H. Brittain, Washington, D.C., May 9, 1999.

Thirteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *Crystallization in the Pharmaceutical Sciences Short Course: "Analytical Methods for Determining the Progress and Outcome of Crystallization"* and *"Regulatory Considerations"*, San Francisco, November 15-19, 1998.

Thirteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *Characterization of Drug Substances – A Holistic Approach Short Course: "Physical Characterization - Polymorphism"*, San Francisco, November 15-19, 1998.

Nicolet Instruments Research Symposium, *"Pharmaceutical Analysis Utilizing IR and Raman Spectroscopy"*, Chicago, IL/Boston, MA/Philadelphia, PA/Washington, D.C./San Francisco, CA, October 20, November 3, December 3, 10, and January 28, 1998-9.

The Twenty-Fifth International Symposium on Controlled Release of Bioactive Materials, Workshop: Crystallization and Polymorphism Issues in Controlled Release Dosage Forms, *"Methods of Analysis - Spectroscopic Techniques"* and *"Advanced Issues - Mixture Analysis"*, Las Vegas, NV, June 25-26, 1998.

Nicolet Instruments Research Symposium, *"Analysis of Pharmaceutical Materials Through a Combined Use of Vibrational Spectroscopy Techniques"*, Washington, D.C./Philadelphia, PA/Boston, MA/San Francisco, CA/Denver, CO, November 13, December 2, 9, 16, and January 22, 1997-8.

Twelveth Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *Revolutions in Stability Testing Symposium: "A Summary of Analytical Techniques for the Physical Stability Testing of Solids"*, Boston, MA, November 2-6, 1997.

NYC Section - American Chemical Society Analytical Topical Group Meeting, *Selected Applications of Raman Spectroscopy in the Pharmaceutical Industry*, New York, October 9, 1997.

The 134th British Pharmaceutical Conference, *Polymorphism Symposium: "Spectroscopic Techniques - Case Examples in Practice"*, Scarborough, UK, September 15-18, 1997.

The Eighth International Symposium on Pharmaceutical and Biomedical Analysis, *"Solid-State Spectroscopic Techniques for the Study of Pharmaceutical Solids"*, Orlando, FL, May 4-7, 1997.

Thirtieth Annual Higuchi Research Seminar, *"A Multi-Disciplinary Approach to Pharmaceutical Solids Characterization"*, Lake Ozark, MO, March 9-12, 1997.

Nicolet Instruments Research Symposium, *"Analysis of Pharmaceutical Materials Through a Combined Use of Vibrational Spectroscopy Techniques"*, Washington, D.C./Boston, MA/Denver, CO/San Francisco, CA/Philadelphia, PA/Los Angles, CA, October 16, 30, November 6, 20, December 11, and January 15, 1996-7.

AAPS/FDA Workshop on Polymorphism of Drug Substances: Manufacturing, Formulation, Analytical, Stability, Bioavailability, and Regulatory Affairs Issues, planning committee member and invited speaker: *"Quantitative Analysis of Polymorphism in Bulk Drug Substance and Dosage Forms"*, Arlington, VA, February 26-28, 1996.

Nicolet Instruments Research Symposium, *"FT-Raman Applications in the Pharmaceutical Development Laboratory"*, Chicago, IL/Boston, MA/Princeton, NJ/San Francisco, CA/Los Angles, CA, November 2, 7, 9, December 12 and 14, 1995.

PharmAnalysis Conference and Exhibition '94, *"Solid-State NMR: Theory, Experimental, and Selected Pharmaceutical Applications"*, Atlantic City, NJ, June 21, 1994.

Nicolet Instruments User's Meeting, *"A Review of IR Sampling Techniques for Modern Problem Solving and Methods Development"*, Saddlebrook, NJ, October 26, 1993.

SSCI's Pharmaceutical Solids Short Course, *"An Integrated Solid-State IR, Raman, and NMR Approach to Pharmaceutical Solids Characterization"*, yearly participation.

Nicolet Instruments User's Meeting, *"Utilization of Various IR Sampling Techniques for the Qualitative and Quantitative Characterization of Pharmaceutical Polymorphs"*, Somerset, NJ, August 26, 1993.

PharmAnalysis Conference and Exhibition '93, *"IR Sampling Techniques for Modern Problem Solving and Methods Development in the Pharmaceutical Laboratory"*, East Brunswick, NJ, June 14-15, 1993.

Fourth International Symposium on Pharmaceutical and Biomedical Analysis, *"Solid-State NMR and IR for the Analysis of Pharmaceutical Solids"*, Baltimore, MD, April 18-21, 1993.

Seventh Annual American Association of Pharmaceutical Scientists Meeting and Exposition, *"An Integrated Solid State IR and NMR Approach to Polymorph Characterization"*, San Antonio, TX, November 15-19, 1992.

The Midwest Organic Solid State Chemistry Symposium, *"Quantitative Determination of Polymorphism in Fosinopril Sodium Utilizing Solid State NMR and Diffuse Reflectance IR Spectroscopy"*, Purdue University, West Lafayette, IN, June 8-9, 1990.

Federation of Analytical Chemistry and Spectroscopy Society Meeting, *"Chiroptical Studies of Pharmaceutical Compounds"*, Chicago, IL, October, 1989, Submission 207.

Nicolet Instruments Spring Seminar Series, *"Identification and Quantitation of Pharmaceutical Polymorphs"*, New Brunswick, NJ, June, 1989.

PUBLICATIONS

D.E. Bugay and R.C. Brush, *"Chemical Identity Testing by Remote-Based Dispersive Raman Spectroscopy"*, **Appl. Spectrosc.**, 64(5), 467-475 (2010).

D.E. Bugay, J-O. Henck, M.L. Longmire, and F.C. Thorley, *"Raman Analysis of Pharmaceuticals"*, in Pivonka, D.E., Chalmers, J.M., and Griffiths, P.R. (Eds.), **Applications of Vibrational Spectroscopy in the Pharmaceutical Research and Development**, Chichester: John Wiley & Sons, 2007, pp. 239-262.

D.E. Bugay and H.G. Brittain, *"Infrared Absorption Spectroscopy"*, in Brittain, H.G. (Ed.), **Spectroscopy of Pharmaceutical Solids**, New York: Marcel Dekker, 2006, pp. 235-269.

D.E. Bugay and H.G. Brittain, *"Raman Spectroscopy"*, in Brittain, H.G. (Ed.), **Spectroscopy of Pharmaceutical Solids**, New York: Marcel Dekker, 2006, pp.271-312.

I. Ivanisevic, D.E. Bugay, and S. Bates, *"On pattern matching of x-ray powder diffraction data"*, **J. Phys. Chem. B**, 109(16), 7781-7787 (2005).

P.A. Tishmack, D.E. Bugay, and S.R. Byrn, *"Solid-State Nuclear Magnetic Resonance Spectroscopy - Pharmaceutical Applications"*, invited article in **J. Pharm. Sci.**, 92, 577-610 (2003).

D.E. Bugay and P.A. Martoglio-Smith, *"Raman Spectroscopy"*, in Moffat, A.C., Osselton, M.D., and Widdop, B. (Eds.), **Clarke's Analysis of Drugs and Poisons**, 3rd Ed., London: Pharmaceutical Press, 2004, pp. 358-367.

D.E. Bugay and W.P. Findlay, *"Vibrational Spectroscopy"*, in Ohannesian, L.A. and Streeter, A. (Eds.), **Handbook of Pharmaceutical Analysis**, New York: Marcel Dekker, Inc., 2002, pp 501-535.

D.E. Bugay, *"Nuclear Magnetic Resonance Spectroscopy"*, in Ohannesian, L.A. and Streeter, A. (Eds.), **Handbook of Pharmaceutical Analysis**, New York: Marcel Dekker, Inc., 2002, pp 467-499.

D.E. Bugay, *"Characterization of the Solid-State: 2. Spectroscopic Techniques"*, invited article in

Adv. Drug Del. Rev., 48(1), 43-65 (2001).

R.B. Gandhi, J.B. Bogardus, D.E. Bugay, R.K. Perrone, and M.A. Kaplan, *"Pharmaceutical Relationships of Three Solid State Forms of Stavudine"*, **Int. J. Pharm.**, 201, 221-237 (2000).

D.E. Bugay, *"Physical Characterization of Pharmaceutical Solids by Raman Spectroscopy,"* in Biomedical Applications of Raman Spectroscopy, M.D. Morris, Editor, **Proceedings of SPIE,** 3608, 56-63 (1999).

D.E. Bugay and W.P. Findlay, **Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy**, Marcel Dekker, New York, 1999.

D.E. Bugay and W.P. Findlay, **Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy**, Electronic Spectral Library, Nicolet Instruments, Inc., Madison, WI, December 1998.

W.P. Findlay and D.E. Bugay, *"Utilization of Fourier Transform-Raman Spectroscopy for the Study of Pharmaceutical Crystal Forms"*, **J. Pharm. Biomed. Anal.**, 16, 921-93- (1998).

C. Rodriguez and D.E. Bugay, *"Characterization of Pharmaceutical Solvates by Thermogravimetric/Infrared Analysis (TG/IR)"*, **J. Pharm. Sci.**, 86(2), 263-266 (1997).

D.E. Bugay, A.W. Newman, and W.P. Findlay, *"Quantitation of Cefepime 2·HCl Dihydrate in Cefepime 2·HCl Monohydrate by Diffuse Reflectance IR and Powder X-Ray Diffraction Techniques"*, **J. Pharm. Biomed. Anal.**, 15(1), 49-61 (1996).

C.J. Petty, D.E. Bugay, W.P. Findlay, and C. Rodriguez, *"Applications of FT-Raman Spectroscopy in the Pharmaceutical Industry"*, **Spectroscopy**, 11(5), 41-45 (1996).

A.W. Newman, R.L. Mueller, I.M. Vitez, C.C. Kiesnowski, D.E. Bugay, W.P. Findlay, and C. Rodriguez, *"Starch"*, in: Brittain, H.G. (Ed.), **Analytical Profiles of Drug Substances and Excipients.** New York: Academic Press, 1996; Vol. 24, pp 523-577.

D.E. Bugay, *"Magnetic Resonance Spectrometry"*, in **Physical Characterization of Pharmaceutical Solids**, Brittain, H.G. (Ed.), New York: Marcel Dekker, Inc., 1995, pp 93-125.

D.E. Bugay and A.C. Williams, *"Vibrational Spectroscopy"*, in **Physical Characterization of Pharmaceutical Solids**, Brittain, H.G. (Ed.), New York: Marcel Dekker, Inc., 1995, pp. 59-91.

D.E. Bugay, *"Solid-State NMR: Theory, Experimental, and Selected Pharmaceutical Applications"*, in: **Proceedings of the PharmAnalysis '94 Conference**. Atlantic City, NJ: Advanstar Communications, 1994; pp 218-235.

K.R. Morris, A.W. Newman, D.E. Bugay, S.A. Ranadive, A.K. Singh, M. Szyper, S.A. Varia, H.G. Brittain, and A.T.M. Serajuddin, *"Characterization of Humidity-Dependent Changes in Crystal Properties of a New HMG-CoA Reductase Inhibitor in Support of its Dosage Form Development"*, **Inter. J. Pharm**., 108, 195-206 (1994).

A.W. Newman, I.M. Vitez, P. Cortina, G. Young, J. DeVincentis, D.E. Bugay, and T. Patel, *"Talc"*, in: Brittain, H.G. (Ed.), **Analytical Profiles of Drug Substances and Excipients.** New York: Academic Press, 1994; Vol. 23, pp 511-542.

A.W. Newman, I.M. Vitez, P. Cortina, G. Young, J. DeVincentis, D.E. Bugay, and T. Patel, *"Talc"*, in:

Brittain, H.G. (Ed.), **Analytical Profiles of Drug Substances and Excipients.** New York: Academic Press, 1994; Vol. 23, pp 511-542.

H.G. Brittain, K.R. Morris, D.E. Bugay, A.B. Thakur, and A.T.M. Serajuddin, *"Solid-State NMR and IR for the Analysis of Pharmaceutical Solids: Polymorphs of Fosinopril Sodium"*, **J. Pharm. Biomed. Anal.**, 11, 1063-1069 (1994).

D.E. Bugay, W.P. Findlay, and F. Rinaldi, *"A Review of IR Sampling Techniques for Modern Problem Solving and Methods Development in the Pharmaceutical Laboratory"*, in: **Proceedings of the PharmAnalysis '93 Conference**. East Brunswick, NJ: Advanstar Communications, 1993; pp 200-210.

D.E. Bugay, *"Solid State Nuclear Magnetic Resonance Spectroscopy - Theory and Pharmaceutical Applications"*, **Pharm. Res.**, 10(3), 317-327 (1993).

F.M. Wasacz, S.W. Strand, D.E. Bugay, and K.R. Morris, *"The Characterization of the Hydration State of Pharmaceuticals by Variable Temperature Diffuse Reflectance Infrared Spectroscopy"*, Eighth International Conference on Fourier Transform Spectroscopy, H.M. Heisse, E.H. Korie, and H.W. Siesler, Editors, **Proceedings of SPIE**,1575, 305-306 (1992).

H.G. Brittain, S.J. Bogdanowich, D.E. Bugay, J. DeVincentis, G. Lewen, and A.W. Newman, *"Anhydrous Lactose"*, in: Florey, K. (Ed.), **Analytical Profiles of Drug Substances**. New York: Academic Press, 1991; Vol. 20, pp 369-398.

H.G. Brittain and D.E. Bugay, *"Solid-State Properties at the Molecular Level"*, in: **Proceedings of the Pharm Tech Conference '91**. New Brunswick, NJ: Aster Publishing Corp., 1991; pp 519-527.

H.G. Brittain, S.J. Bogdanowich, D.E. Bugay, J. DeVincentis, G. Lewen, and A.W. Newman, *"Physical Characterization of Pharmaceutical Solids"*, **Pharm. Res.**, 8(8), 963-973 (1991).

D.E. Bugay, K.R. Morris, *"Polymorphic Characterization by ^{31}P Solid State NMR"*,**TAMU NMR Newsletter**, 374, 53-54 (1989).

D.E. Bugay, C.H. Bushweller, C.T. Danehey, Jr., S. Hoogasian, J.A. Blersch, W.R. Leenstra, *"A Complementary IR/NMR Approach for the Determination of IR Extinction Coefficients and Thermodynamic Parameters for Conformers in Rapid Equilibrium. The Halocyclohexanes."*, **J. Phys. Chem.**, 93, 3908-3911 (1989).

D.E. Bugay, *"Characterization and Quantification of the Pseudopolymorphs of Aztreonam by ^{13}C CP/MAS"*, **TAMU NMR Newsletter**, 364, 60-61 (1989).

H.G. Brittain, D.E. Bugay, S.J. Bogdanowich, and J. DeVincentis, *"Spectral Methods for Determination of Water"*, **Drug Dev. Ind. Pharm.**, 14(14), 2029-2046 (1988).

D.E. Bugay, *"Quantitative ^{31}P NMR"*, **TAMU NMR Newsletter**, 354, 34-35 (1988).

D.E. Bugay and W.R. Leenstra, *"Conversion of QCFF (QCPE 247) to the VAX 8600 System"*, **QCPE Bulletin**, 7(3), 111-114 (1987).

D.E. Bugay and W.R. Leenstra, *"Excited Triplet State Infrared Spectrometry as an Analytical Technique"*, **Anal. Chem.**, 58, 2335-2337 (1986).

D.E. Bugay and G.A. Pearse, Jr., *"Potentiometric Determination of Equivalent Weight of ortho-*

Substituted Benzonitriles", **Microchem. J.**, 28, 595-599 (1983).

PRESENTATIONS

D.E. Bugay, *"Pharmaceutical Polymorphs"*, **Twenty-fourth Annual Humphrey Memorial Symposium in Chemistry, University of Vermont**, 09/23/05, Burlington, VT.

D.E. Bugay, P.A. Martoglio-Smith, R.L. Te, and M.A. Houghtaling, *"Drug Product Investigations Utilizing Raman Spectroscopy"*, **Twenty-nineth Federation of Analytical Chemistry and Spectroscopy Societies Meeting**, 10/15/02, Providence, RI.

D.E. Bugay, P.A. Smith, M.A. Houghtaling, and A. Park, *"Investigating Drug Delivery Systems by Spectroscopic Mapping Techniques***", Twenty-nineth Meeting and Exposition of the Controlled Release Society Meeting**, 07/24/02, Seoul, Korea.

P.A. Martoglio Smith, B.W. Russell, D.E. Bugay, and C. Rojewski *"The Use of Raman Spectroscopy and Discriminant Analysis to Characterize Crystallization of an Amorphous Drug Substance in Drug Product",* **Thirty-ninth Annual Eastern Analytical Symposium**, 10/31/00, Atlantic City, NJ.

P.A. Martoglio Smith, D.E. Bugay, and M.A. Houghtaling, *"Chemometric Applications of Mixture Analysis using FT-Raman Spectroscopy",* **Twenty-seventh Federation of Analytical Chemistry and Spectroscopy Societies Meeting**, 09/27/00, Nashville, TN.

D.E. Bugay, *"Physical Characterization of Pharmaceutical Solids by Raman Spectroscopy"*, **BiOS '99**, 01/25/99, San Jose, CA.

D.E. Bugay, *"Physical Characterization of Pharmaceutical Solids by Raman Spectroscopy",* **Twenty-fifth Federation of Analytical Chemistry and Spectroscopy Societies Meeting**, 10/15/98, Austin, TX.

R.L. Mueller, A.W. Newman, I.M. Vitez, C. Kiesnowski, D.E. Bugay, and W.P. Findlay, *"Scanning Electron Microscopy as a Problem Solving Tool"*, **Thirty-sixth Eastern Analytical Symposium**, 11/16/97-11/21/97, Somerset, NJ.

D.E. Bugay, W.P. Findlay, and F. Rinaldi, *"A Multi-Disciplinary, Molecular Spectroscopy Approach to Pharmaceutical Solids Characterization"*, **Twenty-Sixth Annual Meeting of the Fine Particle Society**, 8/23/95 - 8/24/95, Chicago, IL.

F. Rinaldi, D.E. Bugay, K.R. Morris, and G. Addona, *"Quantitative Analysis of Polymorphism in Fosinopril Sodium Utilizing ^{13}C and ^{31}P Solid-State NMR Spectroscopy"*, **Thirty-third Eastern Analytical Symposium**, 11/13/94-11/18/94, Somerset, NJ.

W.P. Findlay and D.E. Bugay, *"Hot-Stage Infrared Microspectroscopy for the Study of Pharmaceutical Polymorphs"*, **Twenty-first Federation of Analytical Chemistry and Spectroscopy Societies Meeting**, 10/2/94-10/7/94, St. Louis, MO.

A.W. Newman, P. Cortina, J. DeVincentis, I. Vitez, S.A. Ranadive, F. Rinaldi, and D.E. Bugay, *"Pharmaceutical Solid and Particulate Characterization During Drug Development"*, **Twenty-fifth Annual Meeting of the Fine Particle Society**, 7/25/92-7/28/94, East Brunswick, NJ.

K.R. Morris, A.W. Newman, and D.E. Bugay, *"The Energetic and Structural Effect of Partial Size on the Characterization of Pharmaceutical Solids"*, **Twenty-third Annual Meeting of the Fine Particle Society**, 7/13/92-7/17/92, Las Vegas, NV.

D.E. Bugay, K.R. Morris, W.P. Findlay, and D.P. Lambarski, *"Where Did The IR Peaks Go? -*

Comparison of Diffuse Reflectance and KBr Pellet Sampling Techniques for Hydrate Characterization by FTIR Spectroscopy", **Sixth National American Association Pharmaceutical Scientists Meeting**, 11/17/91-11/21/91, Washington, D.C., Abstract APQ1001.

H.G. Brittain and D.E. Bugay, *"Solid-State Properties at the Molecular Level"*, **Pharm Tech Conference '91**, 9/23/91-9/25/91, New Brunswick, NJ.

S.W. Strand, D.E. Bugay, and K.R. Morris, *"Applications of FT-IR Reflection Spectroscopy in the Study of Materials at Elevated Temperatures"*, **1991 Pittsburgh Conference**, 3/4/91-3/8/91, Chicago, IL, Abstract 857.

H.G. Brittain, D.E. Bugay, and G.A. Addona, *"Determination of Water in Alkylboronic Acids by CIR-FTIR"*, **Fifth National American Association Pharmaceutical Scientists Meeting**, 11/4/90-11/8/90, Las Vegas, NV, Abstract APQ1123.

D.E. Bugay, *"Pharmaceutical Problem Solving by FTIR Microscopy"*, Spectra-Tech, Inc. User's Meeting, **Sixteenth Federation of Analytical Chemistry and Spectroscopy Scientists Meeting**, Chicago, IL, October, 1989.

POSTER SESSIONS

R.L. Te, P.A. Martoglio-Smith, D.E. Bugay, and C.J. Rojewski, *"Solid-State Form Analysis in Drug Product by FT-Raman Spectroscopy,"* **Sixth International Conference on Pharmacy and Applied Physical Chemistry (Ph and TA 6)**, 06/26/02-06/30/02, Ascona, Switzerland.

D.E. Bugay and M.A. Houghtaling, *"Raman Spectroscopic Imaging – A Potential New Technique for Content Uniformity Testing,"* **Fourteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition**, 11/14/99-11/18/99, New Orleans, LA.

P. McGlynn, M.P. Redmon, S.A. Wald, H.G. Morrison, A.W. Newman, B.W. Russell, G.P. Stahly, D.E. Bugay, L. Li-Bovet, and A.F. Venero, *"Quantitation of Amorphous Material in Micronized Levalbuterol Sulfate,"* **Fourteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition**, 11/14/99-11/18/99, New Orleans, LA.

M.C. Andres, D.E. Bugay, A.T. McKenzie, D.M. Remick, G.P. Stahly, and A.S. Thomas, *"Quantitative X-Ray Powder Diffraction Analysis: A Comparison of Data Analysis Techniques"*, **Thirteenth Annual American Association of Pharmaceutical Scientists Meeting and Exposition**, 11/15/98-11/19/98, San Francisco, CA.

W.P. Findlay and D.E. Bugay, *"Utilization of Fourier Transform-Raman Spectroscopy for the Study of Pharmaceutical Crystal Forms"*, **Tenth National American Association Pharmaceutical Scientists Meeting**, 10/27/96-10/31/96, Seattle, WA, Abstract APQ 1266.

D.E. Bugay, W.P. Findlay, and F. Rinaldi, *"A Review of Vibrational Spectroscopy Techniques and 'Tricks' for the Characterization of Pharmaceutical Solids"*, **Ninth National American Association Pharmaceutical Scientists Meeting**, 11/6/94-11/10/94, San Diego, CA, Abstract AP 1103.

A.B. Thakur, X. Chen, D.E. Bugay, and A.T.M. Serajuddin, *"Solid State Incompatibility of Dicalcium Phosphate Dihydrate with the Sodium Salt of a Poorly Water Soluble Drug"*, **Ninth National American Association Pharmaceutical Scientists Meeting**,11/6/94-11/10/94, San Diego, CA, Abstract PT6143.

K.R. Morris, A.W. Newman, D.E. Bugay, S.A. Ranadive, M. Szyper, S.A. Varia, H.G.Brittain, and A.T.M. Serajuddin, "*Humidity-Dependent Changes in Crystalline Properties of an Organic Hydrate*

in Bulk Material and in Solid Dosage Forms", **Sixth National American Association Pharmaceutical Scientists Meeting**, 11/17/91-11/21/91, Washington, D.C., Abstract PT6082.

F.M. Wasacz, S.W. Strand, D.E. Bugay, and K.R. Morris, *"The Characterization of the Hydration State of Pharmaceuticals by Variable Temperature Diffuse Reflectance Infrared Spectroscopy"*, **Eighth International Conference on Fourier Transform Spectroscopy**, 9/1/91-9/6/91, Lübeck-Travemünde, Germany, Paper 143.

H.G. Brittain, S.J. Bogdanowich, A.W. Newman, J. DeVincentis, and D.E. Bugay, *"Physical Characterization of Magnesium Stearate"*, **Fifth National American Association Pharmaceutical Scientists Meeting**, 11/4/90-11/8/90, Las Vegas, NV, Abstract PT6159.

K.R. Morris, D.E. Bugay, A. Serajuddin, H.G. Brittain, A. Thakur, S.J. Bogdanowich, and J. DeVincentis, *"Investigation of Polymorphism of Fosinopril Sodium, A New ACE Inhibitor"*, **Fourth National American Association Pharmaceutical Scientists Meeting**, 10/22/89-10/26/89, Atlanta, GA, Abstract PD895.

D.E. Bugay, K.R. Morris, H.G. Brittain, *"Quantitative Determination of Polymorphism in Fosinopril Sodium by ^{31}P and ^{13}C Solid State NMR Spectroscopy"*, **Sixteenth Federation of Analytical Chemistry and Spectroscopy Scientists Meeting**, 10/01/89-10/06/89, Chicago, IL, Submission 25.

D.E. Bugay, K.R. Morris, and H.G. Brittain, *"Quantitative Determination of Phase Composition in Fosinopril Sodium using Solid State NMR Spectroscopy"*, **Third National American Association Pharmaceutical Scientists Meeting**, 10/31/88-11/3/88,Orlando, FL, Abstract AP355.

H.G. Brittain, D.E. Bugay, and S.J. Bogdanowich, *"Spectroscopic Characterization of the Pseudopolymorphs of Aztreonam"*, **Third National American Association Pharmaceutical Scientists Meeting**, 10/31/88- 11/3/88, Orlando, FL, Abstract AP356.