

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KINDERFARMS, LLC,
Petitioner,

v.

GENEXA, INC.
Patent Owner.

Case No. PGR2023-00051
U.S. Patent No. 11,617,795

**DECLARATION OF DR. CORY J. BERKLAND IN SUPPORT OF
PATENT OWNER'S RESPONSE TO PETITION**

TABLE OF CONTENTS

	Page
I. INTRODUCTION AND QUALIFICATIONS	1
A. Qualifications and Experience	1
B. Compensation	5
C. Materials Considered	5
II. PERSON OF ORDINARY SKILL IN THE ART	6
III. SUMMARY OF OPINIONS	8
IV. STATEMENT OF LEGAL PRINCIPLES	8
A. Claim Construction	8
B. Standard for Obviousness	9
V. BACKGROUND	11
A. Genexa and its Agave-Based Kids' and Infants' Pain & Fever Products	11
B. The Characteristics of Agave	13
C. Viscosity of Liquid Pharmaceutical Formulations	17
1. Viscosity Generally	17
2. Acceptable Viscosities of Liquid Pharmaceutical Formulations	17
3. The Amount of Water Substantially Impacts the Viscosity of Liquid Pharmaceutical Formulations Containing Polyols and/or Sugars	19
VI. THE '795 PATENT	20
VII. ALLEGED PRIOR ART ASSERTED BY PETITIONER	29
A. FR485 (Ex. 1004)	29
1. FR485-Example 1	32
B. The '4666 Patent (Ex. 1005)	33
C. WO133 (Ex. 1006)	36

TABLE OF CONTENTS
(continued)

	Page
D. WO742 (Ex. 1007)	39
VIII. CLAIM CONSTRUCTION: “AGAVE SYRUP”	42
IX. NON-OBVIOUSNESS OF THE ’795 PATENT	43
A. Agave-based Formulations with the Claimed Viscosity Are Not Obvious in light of Grounds 1 and 2	43
1. Petitioner and Dr. Crowley Rely on an Incorrectly Cited Viscosity Value for Agave Syrup	44
2. Petitioner Fails to Address the Obvious Error in the ’4666 Patent	49
3. A POSA Would Not Combine the non-overlapping viscosity ranges of the ’4666 Patent and WO133	53
B. Ground 1 Fails to Render Obvious the Claims of the ’795 Patent	54
1. Ground 1 Also Does Not Render the Dependent Claims as Obvious	61
2. Dependent Claims 2-4, 15, & 19	62
3. Dependent Claims 5, 6, & 8	62
4. Dependent Claim 9	63
5. Dependent Claims 13 & 24	64
C. Ground 2 Fails to Render Obvious the Claims of the ’795 Patent	65
1. Ground 2 Also Does Not Render the Dependent Claims as Obvious	68
2. Dependent Claims 2-4 & 15	68
3. Dependent Claims 5-6	69
4. Dependent Claim 9	70
5. Dependent Claim 13	71

TABLE OF CONTENTS
(continued)

	Page
D. It Is Unnecessary to Address Petitioner’s “Alternative” Ground 3	71
X. CONCLUSION.....	72
XI. CERTIFICATION	73

INDEX OF EXHIBITS

Exhibit	Description of Document
2001	<i>Genexa Launches First-to-Market Clean Over-the-Counter Medicine</i> , BusinessWire (Sept. 29, 2020)
2002	Patent Trial and Appeal Board Consolidated Trial Practice Guide (November 2019)
2003	Declaration of Adam M. Pivovar in Support of Motion to Appear <i>Pro Hac Vice</i>
2004	Biography of Adam Pivovar
2005	Declaration of Stephen Smith in Support of Motion to Appear <i>Pro Hac Vice</i>
2006	Biography of Stephen Smith
2007	Declaration of Brianna (Chamberlin) Patterson in Support of Motion to Appear <i>Pro Hac Vice</i>
2008	Biography of Brianna (Chamberlin) Patterson
2009	Declaration of Dr. Cory J. Berkland in Support of Patent Owner's Response to Petition
2010	Genexa Kids' Pain & Fever Blueberry Flavor, available at https://www.businesswire.com/news/home/20200929005330/en/
2011	September 2021 OTC Product News, Infants' Pain and Fever, <i>Pharmacy Times</i> , 87:9 (2021), available at https://www.pharmacytimes.com/view/september-2021-otc-product-news
2012	E. Mellado-Mojica and M. G. Lopez, Identification, classification, and discrimination of agave syrups from natural sweeteners by infrared spectroscopy and HPAEC-PAD, <i>Food Chemistry</i> , 167, 349-357 (2015)
2013	B.I. Maldonado-Guevara et al., Production Process Effect on Mexican Agave Syrups Quality: A Preliminary Syrup, <i>J. Food Res.</i> , 7:3 (2018)
2014	E. Hill et al., Sweetener Content of Common Pediatric Oral Liquid Medications, <i>Am. J. Hosp. Pharm.</i> 45:135-42 (1988)

INDEX OF EXHIBITS
(continued)

Exhibit	Description of Document
2015	SCOGS (Select Committee on GRAS Substances) Database, FDA available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=SCOGS
2016	Combined Index to USP 40 and NF 35, Volumes 1-4
2017	Search Results for “agave,” Combined Index to USP 40, available at: https://www.usp.org/search?search_api_fulltext=agave .
2018	Search results for “agave syrup,” Merck Index Online, available at: https://merckindex.rsc.org/search-results?q=agave+syrup
2019	L. Hernandez-Ramos et al., Nutritional value and antioxidant activity of the maguey syrup (<i>Agave salmiana</i> and <i>A. mapisaga</i>) obtained through three treatments, <i>Not. Bot. Horti. Agrobi.</i> , 48:3, 1306-1316 (2020)
2020	P. Subramaniam and N. Nandan, Cariogenic Potential of Pediatric Liquid Medicaments— An <i>in vitro</i> Study, <i>J. Clinical Pediatric Dentistry</i> , 36:4, 357-362 (2012)
2021	U.S. Patent No. 10,238,640
2022	J.F. Swindells et al., Viscosities of Sucrose Solutions at Various Temperatures: Tables of Recalculated Values, <i>Supplement to National Bureau of Standards Circular</i> , 440 (1958)
2023	D. Reker et al., “Inactive” ingredients in oral medications, <i>Sci. Transl. Med.</i> , 11:483 (2019)

I, Dr. Cory J. Berkland, declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

1. I, Cory J. Berkland, Ph.D., have been retained by counsel for Genexa Inc. (“Genexa”) as a technical expert in *KinderFarms LLC v. Genexa Inc.*, No. PGR2023-00051, in which I understand KinderFarms is challenging the patentability of claims 1-24 of U.S. Patent No. 11,617,795 (the “’795 patent”).

2. I have been asked by Genexa’s counsel to assess whether, based on the available prior art, the claimed invention obvious to a person of ordinary skill in the art (“POSA”) at the priority date of the ’795 patent. In my opinion, and as I detail in this Declaration, the prior art presented by KinderFarms does not render any of the Asserted Claims as obvious.

A. Qualifications and Experience

3. Below I summarize my background, qualifications, and experience relevant to the issues raised in the current case. A copy of my curriculum vitae, which includes a full description of my background qualifications is attached to this report as **Appendix A**.

4. Currently, I am a Professor of Biomedical Engineering in the McKelvey School of Engineering and a Professor of Chemistry in the School of Arts and Sciences at Washington University in Saint Louis.

5. I teach courses to undergraduate and graduate students at Washington

University on pharmaceutical formulation and drug delivery. I have taught these courses for approximately 20 years. Previously, I was the Solon E. Summerfield Distinguished Professor of Pharmaceutical Chemistry and of Chemical and Petroleum Engineering at The University of Kansas. I also had an appointment in the Chemistry Department at The University of Kansas that allowed me to serve as an advisor for their graduate students.

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

7. I have worked in the area of pharmaceutical formulations for more than 20 years. I have extensive experience in the area of pharmaceutical delivery design including formulation and analysis. I have also published many review and original articles regarding pharmaceutical formulations as set forth in my curriculum vitae.

8. In my work, I have designed and optimized oral dosage forms, including liquid suspensions. Additionally, I have routinely performed formulation delivery testing on oral dosage forms, including liquid suspensions, which routinely involves viscosity measurements. I have published more than 200 peer-reviewed papers and I have presented my research at many national and international research

conferences and to pharmaceutical and biotechnology companies, including more than 85 invited talks. I have also given distinguished lectures such as the Nagai Foundation Distinguished Lectureship in Japan and a lectureship at the Center of Excellence in Nanotechnology at the Massachusetts Institute of Technology.

9. I currently serve on the editorial advisory board for the peer-reviewed journals Molecular Pharmaceutics and Journal of Pharmaceutical Sciences. In the past, I have served on the editorial advisory board for the Journal of Pharmaceutical Innovation and Therapeutic Delivery. I also currently serve on advisory boards for the Center for Cancer Engineering at The Ohio State University, the Center for Convergence of Bioscience and Medicine at the University of Alabama, and Kansas University Innovation Center at the University of Kansas. I previously served on advisory boards for the Drug Discovery and Development of Experimental Therapeutics program and the National Institutes of Health Pharmaceutical Aspects of Biotechnology training grant program at The University of Kansas.

10. I have received funding for my research from organizations such as the National Institutes of Health, the National Science Foundation, the Department of Defense, the Department of Energy, the Defense Threat Reduction Agency, the PhRMA Foundation, the Coulter Foundation, the American Heart Association, the Cystic Fibrosis Foundation, the Helmsley Foundation, the Juvenile Diabetes Research Foundation, several other philanthropic organizations, and multiple

pharmaceutical companies.

11. Over the years, I have been actively involved in a number of professional societies including the American Association of Pharmaceutical Scientists, the American Institute of Chemical Engineers, the Controlled Release Society, and the American Chemical Society. I have also been elected Fellow of the American Institute for Medical and Biological Engineering and was elected to the National Academy of Inventors. As part of these organizations, I have helped organize and lead (as a chair or co-chair) scientific sessions, including sessions on drug formulation and delivery.

12. I have received numerous awards in recognition of my research, including the Coulter Translational Research Award. The Coulter Translational Research Award is a grant given to researchers who are developing a product as part of their research. At The University of Kansas, I have received major research awards such as the University Scholarly Achievement Award, the Jim Baxendale Commercialization Award, the Leading Light Award, and the Miller Professional Development Award for Research, and I was named a Bellows Scholar in the School of Engineering at The University of Kansas. I have also received the W.T. Kemper Fellowship for teaching excellence at The University of Kansas.

13. I have been granted multiple patents and have co-founded several companies: Orbis Biosciences (sold to Adare Pharmaceuticals), Savara

Pharmaceuticals (NASDAQ: SVRA), Orion BioScience, Kinimmune, and Bond Biosciences. I have held executive positions at each of these companies and I am currently the Chief Scientific Officer and Chairman of the Board at Bond Biosciences and the Chief Executive Officer of Kinimmune.

14. At Orbis Biosciences, where I was the Co-founder and Chief Scientific Officer from 2007-2020, I worked on developing microencapsulated formulations of over-the-counter drugs to create long-acting, taste-masked, pharmaceutical products.

15. I have worked as a consultant in the pharmaceutical industry providing formulation advice to multiple major pharmaceutical and biotechnology companies.

B. Compensation

16. I am being compensated at my normal consulting rate for my work, which is \$850 per hour. My compensation is not dependent on, and in no way affects, the substance of my opinions in this Declaration.

C. Materials Considered

17. The analysis that I provide in this Declaration is based on my education, research, and experience, as well as the documents I have reviewed and considered. In forming my opinions, I have read and considered U.S. Patent No. 11,617,795 (“’795 patent”) and its prosecution history. I have also reviewed the documents described in the Index of Exhibits, the Petition, Dr. Crowley’s Declaration, and the

Institution Decision as well as the documents cited to herein.

18. In forming my opinions, I have also considered the perspective of a POSA as of June 8, 2021, including the knowledge available to a POSA as of that date, and how a POSA would have read and understood the literature pertinent to the invention claimed in the '795 patent.

II. PERSON OF ORDINARY SKILL IN THE ART

19. I understand that an evaluation of the claims of the '795 patent should be undertaken from the perspective of a person of ordinary skill in the art as of the earliest priority date. For purposes of my Declaration, I have assumed that date to be June 8, 2021, the filing date of U.S. Application No. 17/342,414 to which the '795 patent claims priority.

20. I have also been advised that to determine the appropriate level of a POSA, the following factors may be considered: (1) the types of problems encountered by those working in the field and prior art solutions thereto; (2) the sophistication of the technology in question, and the rapidity with which innovations occur in the field; (3) the educational level of active workers in the field; and (4) the educational level of the inventor.

21. In my opinion, and in agreement with the Patent Owner's proposed definition, a POSA would have a bachelor of science degree in a relevant life sciences field, such as chemistry, biochemistry, or pharmacy, with at least two years

of work or laboratory experience in pharmaceutical formulations, and access to one or more team members having experience in pharmaceutical formulation and pharmaceutical regulatory approves, or, in the alternative, at least three to four years of work or laboratory experience in pharmaceutical formulations, and access to one or more team members having experience in pharmaceutical formulation and pharmaceutical regulatory approvals.

22. Dr. Crowley has opined that a POSA “would have a Bachelor of Science degree in a life sciences discipline relevant to the pharmaceutical sciences, such as chemistry, biochemistry, biology or pharmacy” and that a POSA “with a BS degree would likely have work experience or other laboratory experience.” (Ex. 1003 at ¶91.) Dr. Crowley also opined that a POSA “could also have an advanced degree in a relevant life sciences discipline, but, in that case, the person would have less work or laboratory experience” or that alternatively a POSA “may be a person without a BS degree, provided that the individual has several years of experience in the pharmaceutical industry and/or working in a laboratory.” (*Id.*) Additionally, Dr. Crowley opines that a POSA “may work alone or as part of a team developing pharmaceutical formulations.” (*Id.*)

23. I understand that the Board’s institution decision adopted Patent Owner’s proposed definition of a POSA, which I describe above. (Institution Decision (“Inst. Dec.”), Paper 8 at 6-7.) That being said, whether the Petitioner or

the Patent Owner's definition of a POSA is selected would not alter the level of skill to an extent that would change any of my opinions herein.

III. SUMMARY OF OPINIONS

24. I have considered opinions of Dr. Michael Crowley, as set forth in his September 25, 2023 declaration ("Crowley Declaration") (Ex. 1003) and the documents cited therein. I submit this Declaration to respond to opinions offered by Dr. Crowley.

25. It is my opinion that the claims 1-24 of the '795 patent are not obvious in view off any of the alleged prior art or combinations of prior art at issue in KinderFarms' two obviousness "Grounds" in this proceeding.

IV. STATEMENT OF LEGAL PRINCIPLES

26. I am not an attorney and do not provide any opinions regarding the law. I understand that the issues presented in this PGR must be considered in view of particular legal standards. I have been informed by Patent Owner's counsel of certain legal principles that relate to patent invalidity and validity to guide my analysis. I provide a summary of these relevant legal principles below.

27. I understand the burden of proving unpatentability of the '795 patent rests with KinderFarms in this proceeding.

A. Claim Construction

28. For the purposes of this Declaration, I have been informed by counsel

that the claims do not need to be construed in order to resolve the challenges presented by Petitioner. I've also been informed that the Board accepts that express construction is not required at this point in the proceedings, as none of the terms are in controversy. (*See* Inst. Dec. at 7.) However, I have been asked by counsel to opine on the meaning of "agave syrup" as a POSA reading the '795 patent would understand it.

29. I understand that a purpose of claim construction is to determine what a person of ordinary skill in the art would have understood the claim terms to mean. Claim terms are generally given their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art. I understand that the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.

B. Standard for Obviousness

30. I understand from counsel that a patent claim is unpatentable under 35 U.S.C. § 103 if, as of the effective filing date, it would have been obvious to a person having ordinary skill in the field of the technology (the "art") to which the claimed subject matter belongs.

31. I understand that in making an obviousness inquiry, the following *Graham* factors should be considered: (1) the scope and content of the prior art; (2)

the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art, and (4) any indicia of non-obviousness.

32. I understand from counsel that the Petitioner in a PGR bears the burden of proving the obviousness of the claimed invention.

33. I also understand that this requires showing that the combination discloses the claimed invention “as a whole.” I understand that this means the Petitioner must provide an articulated reasoning for combining elements from the prior art such that the combination would arrive at the invention recited in a patent claim. For example, the patent challenger must show that a POSA would have had a reason, suggestion, or motivation to combine those references, and, in making that combination, a POSA would have a reasonable expectation that the combination would be successful.

34. I also further understand from counsel that a combination of prior art references may render a claim obvious if, at the time of the invention, a POSA would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.

35. Conversely, I have been informed that if there was no motivation to combine disclosures from different references, there is no reasonable expectation of success in combining the references, or if the prior art provides information that would have taught away from the combination or would have indicated that the

proposed combination would not be expected to achieve success, then the patent claim is not obvious.

36. I further understand a POSA should not consider what is known today or what was learned from the asserted claims when evaluating obviousness. I understand it is inappropriate to use the patent claims as a template and applying prior art with hindsight to the patent claims by and simply identified elements of the claims from within different references in the prior art without any articulated reasoning for doing so without knowledge of the patent claims. That is, I understand that it is improper to use the invention as a roadmap to find its prior art components, because the approach discounts the value of combining various existing features or principles in a new way that achieves an overall new result.

37. I further understand from counsel that typographical or similar errors in the prior art that would be apparent to a POSA cannot be said to disclose subject matter and therefore cannot be relied on for a determination of obviousness. I understand that typographical errors are not limited to merely errors such as spelling mistakes but encompass any type of transcription errors.

V. BACKGROUND

A. Genexa and its Agave-Based Kids' and Infants' Pain & Fever Products

38. I understand that Genexa was launched in 2017 by founders Max

Spielberg and David Johnson with the goal of providing over-the-counter medicine free of artificial inactive ingredients.

39. Genexa saw a need for clean medicine as consumers have become more conscious of how products impact their health and wellness in recent years, with many looking for all-natural or “clean” products, including food skincare products and over-the-counter medicines. The need for clean over-the-counter pharmaceutical products was especially warranted since nearly all over-the-counter medicines contain ingredients that are known to cause allergic reactions or irritations, including artificial inactive ingredients such as aspartame, propylene glycol, and artificial colorings. (Ex. 2023 at 1, 5.)

40. With the goal of offering “clean” medicines in mind, Genexa developed Kids’ and Infants’ Pain & Fever Products utilizing only six (6) ingredients: acetaminophen, organic agave syrup, organic flavor, citrus extract, non-GMO flavor, and purified water. The agave syrup is used to suspend the active ingredient acetaminophen and mask its bitter taste. The use of agave syrup also allows for more accurate dosing and increased stability of the product.

41. On September 29, 2020 Genexa issued a press release announcing its agave-based acetaminophen formulation under the name “Genexa® Kids’ Pain & Fever.” (See Ex. 2001 at 2); Ex.2010.) Genexa then announced its “Genexa® Infants’ Pain & Fever” agave-based acetaminophen formulation in September 2021.

(See Ex. 2011 at 1.)

42. Despite Dr. Crowley's statement that others had addressed the issue of providing a liquid pharmaceutical formulation primarily containing natural inactive ingredients, I am unaware of any over-the-counter acetaminophen formulations with only natural inactive ingredients prior to the launch of Genexa's products. (See Ex. 1003 at ¶25 n.2.)

B. The Characteristics of Agave

43. Agave syrup is derived from the sap of agave plants and is known as a natural sweetener for food products. It be used to replace other sweeteners like corn syrup or table sugar. (Ex. 2012 at 349 (E. Mellado-Mojica and M. G. Lopez, Identification, classification, and discrimination of agave syrups from natural sweeteners by infrared spectroscopy and HPAEC-PAD, *Food Chemistry*, 167, 349-357 (2015)).)

44. As Dr. Crowley states in his Declaration, agave syrup, also known as agave nectar, can be obtained from various species of agave. (Ex. 1003 at ¶51; Ex. 1027 at 22; Ex. 1023 at 55.) As a naturally-derived product from various agave species grown in different habitats and manufactured in a variety of different processing steps and conditions, agave syrups are diverse in their quality and compositions: "*The variability of production methods, kind of agave, growing agave's region, and part of the plant used in the production process (sap, leaves*

or pine), generates a wide range of products sold under the name of agave syrup.”

(Ex. 2013 at 50-51 (Maldonado-Guevara, Production Process Effect on Mexican Agave Syrups Quality: A Preliminary Study, *J. Food Res.*, Vol. 7, No. 3 (2018)); *see also id.* at 50 and Fig. 1 (describing different processes for producing agave syrup).)

45. Arising from this diversity, analyses performed on a variety of different agave syrups have shown them to have “[a] ***wide variability of physicochemical quality parameters.***” (*Id.* at 56.) It was also recognized in the art that agave syrups are not well known, but rather that “[f]urther analysis of a wide range of syrups . . . ***are needed*** to get more information for a deeper characterization of agave syrups.” (*Id.* at 50.)

46. In contrast to other sweeteners such as aspartame, sucrose, sucralose, sorbitol, and xylitol, all which have widely understood and consistent, physical, chemical properties, agave syrup is not a commonly known excipient for pharmaceutical formulations. (Ex. 2014 at Abstract (E. Hill et al., Sweetener Content of Common Pediatric Oral Liquid Medications, *Am. J. Hosp. Pharm.* 45:135-42 (1988)).) Well-known excipients for pharmaceutical formulations generally have well-defined physical and chemical properties. In this regard, pharmaceutical excipients such as agar, glycerin, propylene glycol, sucrose, or xanthan gum can be found in general pharmaceutical textbooks, the FDA’s

“Generally Recognized As Safe” list of additives, the indexed United States Pharmacopeia or the Merck Index. (See, e.g., Ex. 1029 (Handbook of Pharmaceutical Excipients) at 13-14 (Agar), 283-85 (Glycerin), 592-94 (Propylene Glycol), 703-06 (Sucrose), 782-85 (Xanthan Gum); see also Ex. 1029 at 14 (no entry for “Agave Syrup”); Ex. 2015 (GRAS (no entry for “Agave Syrup”)); Ex. 2016 (USP Combined Index (no entry for “Agave Syrup”)); Ex. 2017 (USP (no search results for “Agave”)); Ex. 2018 (Merck index (no results for “Agave”)).)

47. Agave syrup contains a mixture of components. As noted above, the exact composition of any given agave syrup depends on a variety of different factors, including the species of plant from which the syrup was derived and how it is processed. (Ex. 1007 at 7:5-14; Ex. 1003 at ¶52 (“Agave syrup, which is predominantly composed of fructose and glucose, is a natural sweetener that is slightly sweeter than table sugar. Ex. 1027, at p. 22; Ex. 1008, at p. 2, ¶ 0043.”); Ex. 2012 at 354-55.) For example, in a characterization of various sweeteners, the authors of “Identification, classification, and discrimination of agave syrups from natural sweeteners by infrared spectroscopy and HPAEC-PAD” found that syrup produced from *A. tequilana* contains mostly fructose (>60%) while agave syrup from the *A. salmiana* plant has a higher sucrose content (28-32%). (Ex. 2012 (E. Mellado-Mojica) at 349 (Abstract), 355 (finding “*A. tequilana* contained 24.1-689 mg g⁻¹ of fructose (f.w.), 1.88-186.7 mg g⁻¹ glucose, and trace amounts (<8.82 mg g⁻¹) of

sucrose” compared to the agave syrup from the *A. salmiana* plant “which were mainly composed of sucrose (288-317 mg g⁻¹)”).)

48. “Viscosity is one of the most significant physical chemical properties in determining the quality and acceptability of an [agave] syrup.” (Ex. 1031.) For example, a comparison of agave syrup¹ obtained from two different agave plants (*A. salmiana* and *A. mapisaga*) and three different processing treatments (artisanal evaporation, evaporation under reduced pressure, and lyophilization), the viscosities ranged from 2.05 Pa-s to 15.98 Pa-s, or 2,050 cP to 15,980 cP, respectively. (Ex. 2019 (L. Hernandez-Ramos et al., Nutritional value and antioxidant activity of the maguey syrup (*Agave salmiana* and *A. mapisaga*) obtained through three treatments, *Not. Bot. Horti. Agrobi.* 48(3):1306-1316) at 1311.)

49. Petitioner acknowledges the variability of agave syrup’s properties, including viscosity, describing agave syrup as capable of having a “thinner or thicker consistency.” (Pet. at 15; *see also* Ex. 1007 (agave syrup “can be light to dark in color, thicker or thinner in consistency (viscosity), and even made into powder or crystals if dehydrated totally”).) Petitioner further cites to an exhibit entitled “Rheology of Agave syrup” which reports agave syrup as having a viscosity of 2,560 cP, which is more indicative of a generally thicker consistency. (Ex. 1031.)

¹ The article refers to “maguey syrup” which is just another name for agave syrup.

C. Viscosity of Liquid Pharmaceutical Formulations

1. Viscosity Generally

50. As Dr. Crowley describes, viscosity is the resistance of a fluid to flow. (Ex. 1003 at ¶56; Ex. 1022 at 452-456.) Viscosity can be quantified by the units of pascal seconds (i.e., “Pa s”) or centipoise (“cP”). As a matter of unit conversion, 1 Pa s is equal to 1000 cP.² When a fluid has a higher viscosity, meaning it’s thicker, it exhibits greater resistance to flow. (Ex. 1035 at 470.) Conversely, when a fluid has a lower viscosity, meaning it’s thinner, it exhibits less resistance to flow. (*Id.*) Water is the standard unit for viscosity and has a value of 1 cP. (*E.g., id.* at 471, Table 19-1 (Water: 1.0019 cP at 20° C).)

2. Acceptable Viscosities of Liquid Pharmaceutical Formulations

51. The viscosity of liquid pharmaceutical formulations administered orally varies greatly. Oral liquid formulations of pharmaceuticals can be identified as “solutions, emulsions, suspensions, and extracts.” (Ex. 1012, 745; Ex. 1003, ¶42.) The viscosities of such oral formulations can range from thin solutions with near-water viscosity, low viscosity “elixirs,” as well as “syrups” that “are concentrated, viscous aqueous solutions of sugar or a sugar substitute” (such as glycerin) having

² See <https://www.unitconverters.net/viscosity-dynamic/pascal-second-to-centipoise.htm>.

varying viscosities including highly thick, but still pourable, up to, for example, 4,500 cP. (*See, e.g.*, Ex. 1012, 757 (“The main ingredients in elixirs are ethanol and water”); Ex. 2021, 8:17-21 (“about 1500 to 4500 cPs”).)

52. In an article by Subramaniam and Nandan entitled “*Cariogenic Potential of Pediatric Liquid Medicaments– An in vitro Study*,” the authors assessed the physical properties of various approved and commercially-available pediatric liquid medicines, including the viscosity. Calpol, a paracetamol (acetaminophen) liquid suspension, was found to have a viscosity of 2040 cP. (Ex. 2020 at 359 (Table 1).) Ibugesic, an ibuprofen-based analgesic, has a reported viscosity of 1800 cP. (*Id.*)

Pediatric Liquid Medicaments

Table 1. Mean pH and Viscosity of Paediatric Liquid Medicaments

PLM	PRINCIPAL INGREDIENT	TRADE NAME	PHARMACEUTICAL COMPANY	pH Mean±SD	Viscosity(cP) Mean±SD
Analgesic	Paracetamol	Calpol	Glaxo Smithkline Pharmaceuticals Limited	6.08±0.04	2040.00±10.00
Analgesic	Ibuprofen	Ibugesic	CIPLA Ltd.	4.57±0.02	1800.00±20.00

Chricof, an antitussive formulation, had a viscosity of 1755 cP.

Antitussive	Dexamethorphan Hydrobromide, Chlorpheniramine maleate, Phenylephrine hydrochloride	Chericof	Sobrex Pharmaceuticals Company (for Ranbaxy Laboratories Limited)	4.66±0.01	1755.00±5.00
-------------	--	----------	---	-----------	--------------

(Ex. 2020 (Subramanian) at 359 (excerpted).)

53. Other references also describe oral formulations of acetaminophen as having higher, desirable viscosities. For instance, U.S. Patent No. 10,238,640

discloses pharmaceutical formulations, including those containing acetaminophen, where an “exemplary embodiment of the pharmaceutical composition” would have a “disturbed viscosity (e.g. viscosity measured after mixing under specified conditions) at 25° C. [of] about *1500 to about 4500 cps.*” (Ex. 2021 at 8:17-21 (emphasis added).)

54. Despite these teachings, Dr. Crowley contends that “[g]enerally, suspensions having a viscosity in the range of 20 to 150 cP are considered readily pourable” and that “having a higher viscosity is generally not desirable.” (Ex. 1003 at ¶59.) This is particularly true, according to Dr. Crowley, considering that “increasing the viscosity of a suspension formulation has been shown to impair the dissolution characteristics of immediate release acetaminophen.” (*Id.*)

3. The Amount of Water Substantially Impacts the Viscosity of Liquid Pharmaceutical Formulations Containing Polyols and/or Sugars

55. Concentrated and viscous oral liquid formulations of pharmaceuticals are typically based on aqueous solutions of sugar, such as sucrose, or a sugar substitute in the form of a polyol, such as glycerin. (*See* Ex. 1012 at 754 (“Syrups are concentrated, viscous, aqueous solutions of sugar or a sugar substitute . . . making a solution of sucrose In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added”).) The amount of water included within such sugar or glycerin formulations can profoundly impact the viscosity of the

formulations. (*Id.*) For instance, adding water to an aqueous solution of 83% glycerin to achieve a solution of 70% glycerin changes the viscosity from 111.0 cP to 22.94 cP, a decrease of approximately 88 cP. (Ex. 1029 at 284 (Table VI).) Whereas, further addition of water to an aqueous solution of 70% glycerin to 60% glycerin only further decreases the viscosity by 12 cP. A POSA would understand that a similar trend with respect to the decrease in viscosity of aqueous solutions of sugars and polyols would show similar trends in the drop in viscosity as additional water is added (and vice versa). (*See, e.g.*, Ex. 2022 at 5 (75% sucrose: 2,323 cP; 65% sucrose: 146 cP; 55% sucrose: 28.4 cP).) Hence, the amount of water in a formulation can have a profound impact on the formulation's viscosity—i.e., decreasing the viscosity (when water is added) or increasing the viscosity (when water is removed)—and these changes can be highly sensitive to the viscosity and resulting concentration in the amount of the excipients. That is, the amount of water in a formulation needed to achieve “a viscosity in the range of 20 to 150 cP” and therefore be “readily pourable,” according to Dr. Crowley, would be low when the other components of the formulation generally have overall lower viscosities and higher when the other components of the formulation generally have overall higher viscosities.

VI. THE '795 PATENT

56. I understand that U.S. Patent No. 11,617,795 B2 (Ex. 1001 (the “’795

patent”)) entitled “Pharmaceutical Syrup Formulation or Suspension” issued to inventors, and Genexa founders, Max Spielberg and David Johnson. I understand that the ’795 patent is a continuation of application No. 17/342,414, filed on June 8, 2021, which is a continuation-in-part of application No. 16/827,529 filed on March 23, 2020, now abandoned, which is a continuation of application No. 15/912,785 filed on March 6, 2018, now U.S. Patent No. 10,596,266, which claims the benefit of the Provisional Application No. 62/580,648 was filed on November 2, 2017. I understand Genexa contents that each Accused Claim has a priority date at least as early as June 8, 2021.

57. I understand that the ’795 patent relates to stable, pharmaceutical syrup formulations for oral administration that includes pharmaceutical active agents, agave syrup, and a diluent. (Ex. 1001 at 1:31-34.)

58. The background of the ’795 patent describes the state of the prior art at the time of filing and the need for a liquid pharmaceutical formulation containing mostly natural ingredients. (*Id.* at 1:12-28.) It acknowledges that liquid is desirable to provide drugs in a liquid for to children or older persons because such person can have problems swallowing tablets and capsules. (*Id.* at 1:12-14.)

59. The ’795 patent further acknowledges that liquid formulations are well suited for children because the dose can be tailored to a child’s weight and the formulation can be flavored which improves intake by children. (*Id.* at 1:15-20.)

Because the liquid formulations of analgesic and antihistamine active pharmaceutical agents “taste terrible [] pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste.” (*Id.* at 20-24.) The ’795 patent explains that “[n]o liquid medium, primarily of natural ingredients, containing this combination of active agents are available.” (*Id.* at 1:24-26.) Thus the ’795 patent discloses “a need for an improved pharmaceutical suspension or syrup formulation.” (*Id.* at 1:27-28.)

60. The ’795 patent discloses liquid pharmaceutical formulations that contain at a minimum one or more pharmaceutical active agents, agave syrup, and a dilutant. (Ex. 1001 at 1:31-34, 2:1-4.) The formulations may optionally include an acidic preservative, a sweetening agent, and a flavoring or masking agent. (*Id.* at 1:36-39, 2:5-6.)

61. The ’795 patent discloses multiple pharmaceutical active ingredients suitable for use in the formulations of the ’795 patent, including acetaminophen which is specified in the claims. (*See generally* Ex. 1001 at 1:55-62; 3:26-43, cls. 1-24.) The active pharmaceutical agents can be present in the disclosed formulations in amounts between 0.01 to 4 w/w%, or between 0.01 to 5 grams per 100 mL. (*Id.* at 3:8-19.) “The amount of the pharmaceutical active agent in the suspension should be enough to provide a therapeutic amount and a convenient dosage unit.” (*Id.* at 3:10-13.) The ’795 patent notes that “this may vary depending on the

pharmaceutical active agent and amounts are known to those with ordinary skill in the art or are readily available or can be determined using pharmaceutical science.” (*Id.* at 3:16-21.)

62. The '795 patent defines “agave syrup” as “a processed juice obtained from the agave sp. Plant” and defines “syrup” as “a formulation that has a flow without applied pressure and is sticky or tacky to the touch.” (Ex. 1001 at 2:6-11.) The '795 patent discloses embodiments where the pharmaceutical suspension or syrup formulation includes between 50 to 98% w/w, between 65 to 98% w/w, or between 75 to 95% w/w/ of agave syrup. (*Id.* at 2:40-57.) The '795 patent indicates that agave syrup may also serve as a sweetener in the formulation. (*Id.* at 4:17-21.)

63. The '795 patent describes a dilutant, which a POSA would understand could be water as used in the examples of the specification. (Ex. 1001 at 2:40-56, 3:20-34, 4:10-23, 4:42-52, 5:5-31.) The minimum amount of water should be “limited to the amount necessary to hydrate the agave syrup” and “also must provide the suspension with enough aqueous base to impart the desired consistency.” (*Id.* at 4:13-17.) It discloses that the water should be kept as a minimum to also better mask the bitter taste of acetaminophen. (*Id.* at 3:20-23.)

64. For example, the specification describes that the acetaminophen suspension should contain “from about 0.1 to 2 grams of water per 100 ml of suspension” and from “about 5 to 20 grams per 100 mL of suspension if agave syrup

is used as the sweetener.” (*Id.* at 3:20-24, 4:17-21.)

65. The '795 patent also describes a pharmaceutical formulation that “can enhance the taste masking of unpalatable pharmaceutical active agents with generally natural ingredients. (Ex. 1001 at 1:42-44.) It discloses that this can be done with clean inactive ingredients that are “gluten-free non-GMO, and certified vegan” or unnatural ingredients such as “aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other[s].” (*Id.* at 1:44-50.) In one embodiment, the bitter flavor of pharmaceutical active agents can be masked with sweetening agents including sugars such as “xylose, ribose, glucose, mannose, fructose, dextrose, sucrose, and maltose, and sugar alcohols such as sorbitol, xylitol, mannitol” which can range from “0 grams to about 1 gram of sugar sweetener per 100 mL of the suspension.” (*Id.* at 1:60-63.) Natural and artificial flavoring agents may also be used and are generally present in amounts “in the range of from about 0 grams to about 5 grams per 100 mL of the suspension.” (*Id.* at 4:7-10.)

66. The '795 patent discloses that the pharmaceutical formulation or “syrup can have a viscosity of between about 200 and 3500 centipoise at about 2.5 rpm to about 30 rpm as determined by a Brookfield Viscometer at about 22 degrees.” (Ex. 1001 at 2:13-16.) However, it further describes that the formulation can have a viscosity that is “less than 2000 centipoise, less than 1750 centipoise, less than 1500 centipoise, less than 1000 centipoise, less than 750 centipoise, less than 600

centipoise, or less than 500 centipoise.” (*Id.* at 2:23-27.)

67. The ’795 patent discloses one embodiment in which the pharmaceutical formulation can be prepared by mixing the active ingredient(s) with agave and then adding water to achieve the desired consistency. (Ex. 1001 at 4:37-39.) This can be done by adding an amount of agave into a vessel; warming the amount of agave in the vessel; adding an amount of one or more pharmaceutical agents to the warmed agave in the vessel; stirring the contents of the vessel until the contents are mixed; adding diluent through the process to achieve a desired viscosity of less than, e.g, 1500 centipoise, 1000 centipoise, 600 centipoise, or 400 centipoise. (*Id.* at 4:47-53.)

68. Finally, the ’795 patent discloses two example formulations. It first discloses the following acetaminophen suspension:

Example 1		
Acetaminophen Suspension		
Ingredient	Function	Amount (w/w %)
Pharmaceutical Active Agent (e.g., Acetaminophen)	Treatment	1.8
Agave syrup	Base	92
Citrus acid extract	Preservative	0.20
Masking Agent/Blueberry	Flavoring	0.60
Water	Diluent	Remaining

(Ex. 1001 at 5:5-22.)

69. In Example 2, the ’795 patent discloses a formulation wherein “100 mg

of active agent can be added to 100 mL of agave (heated). The mixture is stirred, and water can be added to achieve a desired consistency. Other agents such as sweetening and flavoring agent can be added to the suspension.” (*Id.* at 5:28-32.)

70. To the extent Dr. Crowley maintains that the specification does not provide any information concerning the viscosity of the acetaminophen suspensions described in Examples 1 and 2, a POSA would easily be able to measure the viscosity with reasonable certainty using the method laid out in the ’795 patent and described above.

71. To the extent Dr. Crowley complains that the Example do not indicate what amount of the suspension in the Examples would need to be administered to an individual to deliver a therapeutic dose, the ’795 patent teaches 1.8% w/w of active ingredient within the suspension in Example 1. (Ex. 1001 at Example 1, 5:5-21.) Further, the ’795 patent also teaches that the appropriate dose would be apparent to a POSA. (*Id.* at 3:16-19). Further the dosing information for over-the-counter acetaminophen formulations has been available for decades and would be well-known or readily accessible to a POSA in the field. (*See* Ex. 1016 at 2, 4; Ex. 1017 at 742; Ex. 1018 at 1537.)

72. I understand Petitioner is challenging claims 1-24 of the ’795 patent. The challenged claims of the ’795 patent are recited below:

U.S. Patent No. 11,617,795	
Claim 1	A pharmaceutical syrup formulation for oral administration comprising: (a) acetaminophen, (b) agave syrup, and (c) a diluent, wherein the syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees; wherein the acetaminophen is suspended in the syrup; and wherein the syrup is palatable.
Claim 2	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees.
Claim 3	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 750 centipoise at about 22 degrees.
Claim 4	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 600 centipoise at about 22 degrees.
Claim 5	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 2 grams of acetaminophen is suspended per 100 mL of the syrup.
Claim 6	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 1 grams of acetaminophen is suspended per 100 mL of the syrup.
Claim 7	A stable pharmaceutical syrup formulation for oral administration comprising: (a) acetaminophen; (b) agave syrup; (c) acidic preservative; (d) a flavoring agent, and (e) a diluent, wherein the syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees, and wherein the acetaminophen is suspended in the syrup.
Claim 8	The pharmaceutical syrup formulation of claim 7, wherein the acetaminophen is between 0.01 to 2% of the formulation by weight.
Claim 9	The pharmaceutical syrup formulation of claim 7, wherein the diluent is about 5% of the formulation by weight.

U.S. Patent No. 11,617,795	
Claim 10	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is less than 98% of the formulation by weight.
Claim 11	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is less than 95% of the formulation by weight.
Claim 12	The pharmaceutical syrup formulation of claim 7, wherein the diluent is water.
Claim 13	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is about 95% of the formulation by weight.
Claim 14	The pharmaceutical syrup formulation of claim 7, wherein the acidic preservative comprises citric acid.
Claim 15	The pharmaceutical syrup formulation of claim 7, wherein the composition is a medicinal preparation formulated as a syrup; and wherein the composition has a viscosity from about 1500 centipoise to about 400 centipoise at about 22 degrees.
Claim 16	The pharmaceutical syrup formulation of claim 7, wherein the formulation is orally administered for veterinary and human use.
Claim 17	The pharmaceutical syrup formulation of claim 7, wherein the flavoring agent is a bitter-taste-blocking ingredient.
Claim 18	A stable palatable pharmaceutical syrup formulation for oral administration consisting essentially of: (a) a therapeutically effective amount of acetaminophen; (b) agave syrup; (c) acidic preservative; (d) a flavoring agent, and (e) a diluent, wherein the syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees and the acetaminophen is suspended in the syrup.
Claim 19	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees.

U.S. Patent No. 11,617,795	
Claim 20	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.
Claim 21	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.
Claim 22	The formulation of claim 18, wherein the agave syrup is less than 98% of the formulation by weight.
Claim 23	The formulation of claim 18, wherein the agave syrup is less than 95% of the formulation by weight.
Claim 24	The formulation of claim 18, wherein the agave syrup is about 95% of the formulation by weight.

VII. ALLEGED PRIOR ART ASSERTED BY PETITIONER

73. Petitioner relies on four references in its grounds for obviousness which I have reviewed and analyzed below.

A. FR485 (Ex. 1004)

74. French Patent Publication 2,993,458 (“FR458”) is titled “Liquid Pharmaceutical Preparation for Oral Administration Based on Organic Agave Syrup with a Low Glycemic Index.” (Ex. 1004.)

75. FR458 published on January 24, 2014 from a French Patent application (FR1203629A) that was filed on December 21, 2012. FR458 claims priority to FR1202095, which was filed on July 20, 2012 and published on January 24, 2014 as French Patent Publication 2,993,457. (Ex. 1042.)

76. FR485 describes various liquid pharmaceutical formulations for oral

administration comprising active ingredients and excipients. (Ex. 1004 at p.20, lns.4-10.) FR485 notes that “[e]xcipients are the major component by weight of a preparation.” (*Id.* at p.18, lns.10-12.) FR485 teaches that the active agent ingredients in the pharmaceutical formulation can be, among other things, analgesics such as paracetamol.³ (Ex. 1004 at p.22, lns.127-134.)

77. It also describes that pharmaceutical suspensions and syrups consist of “water, sugar, suspending agents wetting agents, co-solvents, solubilizers, preservatives, flavorings, acid pH modifiers . . . sweetening agents, [and] colorants.” (Ex. 1004 at p.19, lns.46-50.) FR485 specifies that the formulations described are based on the “minimal use of additives” avoiding artificial sweeteners and colorants and including low-glycemic index syrups such as organic agave syrup. (*Id.* at p.20, lns.70-74.)

78. It describes that the use of agave syrup in the disclosed inventions has the benefit of a lower glycemic index. (Ex. 1004 at p.20, lns.58-74.) For example, FR458 states:

The present invention provides pharmaceutical suspensions or syrups for oral administration based on syrups with low glycemic indexes, consisting mainly of certified organic agave syrup alone or in combination with other syrups and of an active ingredient used alone or in combination with at least one suspending agent, with or without gelling agents, without preservatives in the case of single-dose

³ Paracetamol is another name for acetaminophen.

preparations and with preservatives in the case of multi-dose preparations, and of natural flavorings. Natural sweeteners such as Rebaudioside and steviol glycosides may be added, as well as natural colorants.

These formulations are based on the minimal use of additives, avoiding the use of artificial sweeteners and of colorants, and on syrups with a low glycemic index such as organic agave syrup. As a result, these formulations are suitable for people seeking a low sugar intake.

(Ex. 1004 at p.20, lns. 58-74.)

79. FR485 discloses that “[f]ormulations based on natural syrups are not easy to obtain and must be heated to obtain homogenized suspensions.” (Ex. 1004 at p.19, lns.52-53.) To address this difficulty, FR458 provides “a general method for the preparation of suspensions/solutions at room temperature” in conjunction with the use of “xanthan gum and agar-agar in the formulation.” (*Id.* at p.24, lns. 188-197.) FR458 explains that “Agar-agar and xanthan gum are mixed with glycerin in a separate container and mixed with a spatula to provide Solution A” and the “active pharmaceutical ingredient(s) is (are) dispersed or dissolved in agave syrup to make Solution B.” (*Id.*) “Solution A is added to Solution B” and “[w]ater and then the rest of the ingredients are added and mixed and the preparation is placed in vials.” (*Id.*)

80. Although FR458 discloses “agave syrup” within oral pharmaceutical formulations, FR458 does not disclose a specific type of agave syrup that must be used or otherwise was used to practice the “invention” disclosed therein, does not

disclose a viscosity for agave syrup or the viscosity of the agave syrup used in any of the Examples therein, and never mentions anything relating to the viscosity for any syrup formulations disclosed therein including the viscosity of any of the Examples.

1. FR485-Example 1

81. FR485 lists four (4) examples of pharmaceutical formulations and the method of making them. (Ex. 1004 at pp.25-27.) The only example containing paracetamol (also known as acetaminophen) is Example 1, the formulation of which has been reproduced below:

<u>Example 1</u>	
Ingredients	Quantity
Paracetamol	2.5 g
Certified agave syrup	45 g
Xanthan gum	0.4 g
Certified agar-agar	0.2 g
Glycerin	5 g
Sodium citrate	0.5 g
Anhydrous citric acid	0.4 g
Natural strawberry flavoring	0.01 g
Purified water	Up to 100 ml

(*Id.* at p.25.)

82. FR458 explains that Example 1 is formed by combining “Solution A” (xanthan gum, agar-agar, and glycerin) and “Solution B” (paracetamol suspended in agave syrup) together and then “the water is topped up to 100 mL and everything is mixed together.” (Ex. 1004 at pp.24-25, lns.185-200.) The collective mass of each ingredient (other than water) within FR458-Example 1 is 54.01 g (i.e., 2.5 g (paracetamol) + 45 g (agave syrup) + 0.4 g (xanthan gum) + 0.2 g (agar-agar) + 5 g (glycerin) + 0.5 g (sodium citrate) + 0.4 g (anhydrous citric acid) + 0.01 g (flavoring)). Because these ingredients would all be generally expected to have a density higher than water (i.e., above 1 g/cm³), FR458-Example 1 would be at least ~50% water by volume (and almost certainly closer to ~60% water by volume).

83. Notably, Example 1 of FR458 does not disclose the identity or viscosity of the agave syrup used in Example 1 or the viscosity of the formulation itself upon addition of the substantial amount of water to create the 100 mL dose.

B. The '4666 Patent (Ex. 1005)

84. U.S. Patent No. 4,684,666 (the “'4666 patent”) is titled “Stabilized Liquid Analgesic Compositions” and issued on August 4, 1987 from U.S. Patent Application No. 897,803 filed on August 19, 1986. (Ex. 1005.)

85. The '4666 patent discloses ibuprofen syrup formulations where the ibuprofen is suspended in an aqueous liquid having more than 50% by weight of a pharmaceutically acceptable polyhydric alcohol bodying agent; a sweetening agent;

and a pH of higher than 7.0 and below 7.7.” (Ex. 1005 at Abstract; *see also* Ex. 1005 at 2:4-14, 2:22-25, 3:37-45, claim 1.) A critical aspect of achieving the “stabilized liquid ibuprofen syrup” disclosed in the ’4666 patent is the formulations having “a pH of higher than 7.0 and below 7.7.” (*Id.* at Abstract.) As taught in the ’4666 patent, “[i]t is essential to the optimum stability of the final product that the pH be maintained in the alkaline range at all times. An acceptable range is above 7.0 and below 7.7, although best results are achieved at a pH of 7.3 to 7.5.” (*Id.* at 3:37-45.) “In order to maintain this level, an alkalizing agent such as a hydroxide must be used,” with suitable compounds being “potassium hydroxide and sodium hydroxide.” (*Id.*)

86. The ’4666 Patent further teaches the “water compatible bodying agents” require “[s]uitable materials [that] must be capable of being freely incorporated into water without affecting clarity of the resultant suspension or solution.” (*Id.* at 2:44-48.) if also explains that these preferred bodying agents are “polyhydric alcohols,” such as glycerol, sorbitol, mannitol, and propylene glycols. (*Id.* at 2:44-54.) The ’4666 patent states that it is only “permissible to use other materials such as sucrose as an incidental part of the bodying agent component” and that any use of sugars “should not constitute a major part thereof because of the general metabolic undesirability of including larger amounts of sugar and the visual haze that develops in the syrup from its use unless special precautions are taken.”

(*Id.* at 2:59-65.) The '4666 patent further explains that “[a]n important aspect of this invention is the inclusion of a major portion of water compatible material or materials that contribute to a rather heavy and uniform viscosity in the final composition.” (*Id.* at 2:41-44.) Characterizing such compositions as being “moderately viscous syrups” (*id.* at 1:11-12), the '4666 patent teaches that: “Viscosity of the product should be controlled for optimum stability. A viscosity of about 1000 to 3000 centipoise at 20° C., as measured by the Brookfield Synchro-Lectric viscometer, is the preferred range.” (*Id.* at 4:9-17.)

87. The '4666 patent does not disclose the use of agave syrup to suspend any active ingredient. Rather the '4666 patent teaches that “[b]ecause of the stability problems encountered with sucrose, coupled with the general undesirability of using a metabolizable sugar in most patients” the preferred sweetener is artificial sodium saccharin. (Ex. 1005 at 3:54-57.) These artificial ingredients are also shown in the example formulations found in Examples I-IV. (*Id.* at 4:39-6:12.)

88. The '4666 patent has three dependent claims related to viscosity, each modifying the three independent claims (Claims 1, 6 and 7), reproduced below:

- | |
|---|
| <p>9. The syrup of claim 1 wherein the viscosity is about 1000 to 3000 centipoise at 20° C.</p> <p>10. The syrup of claim 6 wherein the viscosity is about 1000 to 3000 centipoise at 20° C.</p> <p>11. The syrup of claim 7 wherein the viscosity is about 100 to 3000 centipoise at 20° C.</p> |
|---|

(Ex. 1005 at 6:62-67.)

C. WO133 (Ex. 1006)

89. WO 95/00133 (“WO133”) is an International Patent Publication titled “Taste-Masked Acetaminophen Suspensions and Methods of Making the Same” that published on January 5, 1995 from PCT application PCT/US94/07037 filed on June 21, 1994. (Ex. 1006.)

90. WO133 relates to acetaminophen compositions “in taste-masked form suitable for oral administration, containing acetaminophen in an aqueous medium.” (Ex. 1006 at 2:14-16.) “The aqueous medium contains a suspension agent for dispersing the acetaminophen and additive agent for decreasing the solubility of the acetaminophen in the aqueous medium to below 1.3% wt.” (*Id.* at 2:19-22.) WO133 also discloses that the additive agent serves to masks the “unpalatable taste of the liquid acetaminophen composition.” (*Id.* at 5:12-16.)

91. To accomplish this, WO133 teaches acidic acetaminophen formulations in which the “acetaminophen solubility is limited by the presence of additive agents, such as sweetening agents.” (*Id.* at 1:6-9.) WO133 teaches that compositions preferably contain “2-5% wt., preferably 2-3% wt. acetaminophen, 30-40% wt., preferably **33-37% water**; 0.15-0.2% wt. dispersant; 0.03-0.1% wt., preferably 0.05-0.1% wt. suspension agent; and 55-65% wt. sweetener. The composition can also contain 0.05-0.1% wt. preservative.” (Ex. 1006 at 8:4-9.)

92. WO133 teaches that “[t]he pH of the acetaminophen composition is held below about 6, and most preferably between about 3.5 and 5.” (*Id.* at 7:20-21.) “The pH is preferably maintained at these levels to sustain a long shelf life since the preservatives usually do not work well in a high pH system.” (*Id.* at 7:21-24.) Each Example contained within WO133 discloses a pharmaceutical formulation with artificial ingredients, including large amounts of sucrose, and having a pH in the range of 4.2-4.4, falling squarely within the preferred pH range. (*Id.* at 9:2-17:3; *see also, e.g., id.* at 9:17 (Example 1: “pH=4.3”), 9:17 (Example 1: pH 4.3), 9:28 (Example 2: “pH adjusted to 4.3”), 10:17 (Example 3: “pH adjusted to 4.2”), 11:5-6 (Example 10: “pH adjusted to 4.2”), 14:3-8 (Example 12: “pH adjusted to 4.2 +/- 0.1”).)

93. The specification teaches that the suspension agent can be “xanthan gum, sodium alginate, carrageenan, carboxymethylcellulose, algin, guar gum, propylene glycol alginate, and mixtures thereof; xanthan gum being preferred.” (*Id.* at 4:18-22.) WO133 also discloses that the suspension agent is preferably accompanied by a dispersant which acts to make the aqueous solution containing the suspension agent homogenous. (*Id.* at 5:1-3.) Dispersants can be glycerin propylene glycol, ethanol and a combination thereof.” (*Id.* at 5:6-8.)

94. The additive agent is “preferably a sweetening agent” such as sucrose, glucose, fructose, lactose, and maltose. (*Id.* at 2:23-25, 6:10-13.) WO133 also

discloses that

Natural and semi-refined sweetening agents such as honey and corn syrups, which are mixtures of sugars with other related compounds, can be used, as well as polymers of sugars such as maltodextrin. Low levels of artificial sweeteners such as aspartame and saccharin can also be used.

(*Id.* at 6:13-18.) WO133 notes that “acetaminophen solubility is limited by the presence of additive agents, such as sweetening agents” and that one purpose of the additive agent is “for decreasing the solubility of the acetaminophen in the aqueous medium to below 1.3% wt.” (Ex. 1006 at 1:6-9, 2:19-22.)

95. WO133 specification does not mention agave syrup. WO133 also discloses examples containing additional ingredients such as flavors, preservatives, and “ingestible acid” used to maintain pH. (*Id.* at 7:5-26.) Each example contained within WO133 discloses a pharmaceutical formulation with artificial ingredients. (*Id.* at 9:2-17:3.)

96. WO133 teaches that the viscosity of an “acetaminophen composition generally ranges from about 200-900 centipoise, preferably from about 300-700 centipoise.” (*Id.* at 10.) However, WO133 provides no disclosure regarding the specific viscosity values for any of the example formulations disclosed therein, instead only generally stating that they are “a viscous suspension.” (*See id.* at 9:16-17 (“[t]he acetaminophen composition obtained was a viscous suspension with a

pH=4.3”), 10:4-5 (“[t]he acetaminophen composition obtained was a viscous suspension with a pH=4.4”).)

D. WO742 (Ex. 1007)

97. WO 2012/018742 (“WO742”) is International Patent Publication No. 2012/018742 entitled “Dextromethorphan Antitussive Compositions” that published on February 9, 2012 from PCT application PCT/US2011/046157 filed on August 1, 2011. (Ex. 1007.) WO742 teaches various oral pharmaceutical compositions containing the active ingredient dextromethorphan and an orally acceptable pharmaceutical carrier. (*Id.* at 1 (Abstract), 3:9-10 (“The field of the invention relates generally to antitussive compositions containing dextromethorphan...”), 9:7-9.) It specifically teaches dextromethorphan pharmaceutical compositions that are free of bromide, polistirex, and sodium. (*Id.* at 9:1-3.)

98. For liquid compositions, the orally acceptable pharmaceutical carrier can include a sweetening agent such as “sucrose, corn syrup, agave nectar, invert sugar, dextrose, aspartame, sorbitol, honey, and magnasweet; and other flavoring agents.” (Ex. 1007 at 13:16-23.) It also discloses that preferably the carrier includes agave nectar. (*Id.*)

99. WO742 describes agave nectar, also known as “agave syrup.” (*Id.* at 7:5-9.) WO742 discloses that “agave syrup is similar to honey in color and texture, but it is not as viscous and flows more easily.” (Ex. 1007 at 5:9-10; *see also* Ex.

1031.) It further discloses that agave syrup may be “light to dark in color, thicker or thinner in consistency (viscosity), and even made into powder or crystals if dehydrated totally.” (Ex. 1007 at 7:20-23.)

100. WO742 provides eighteen (18) examples of pharmaceutical compositions, including both liquid and lozenge compositions. (Ex. 1007 at 20:14-26:7.) Examples I-IX disclose liquid formulations, only two of which contain acetaminophen and are reproduced below.

101. Example V of WO742 is an example of “Liquid Cold & Flu Composition Ingredients Amount/15ml” and is reproduced below:

30	EXAMPLE V. Liquid Cold & Flu Composition Ingredients Amount/15 ml	
	Dose:	
	Dextromethorphan Hydrochloride Monohydrate	18.0 mg
	21	
	Acetaminophen	325 mg
	Doxylamine Succinate	6.25 mg
	Agave nectar	11.0 ml
	Propylene Glycol	777.0 mg
5	Flavorants	0.5 ml
	Ethanol (95%)	1.5 ml
	Polyethylene Glycol (Carbowax 400)	750.0 mg
	Aspartame	23.3 mg
	FD & C Red #40	5.1 mg
10	Water, Purified q.s.	

(*Id.* at 21:30-22:10.)

102. Example IX of WO742 is an example of “Liquid Cough Composition

Ingredients Amount/15 mL Dose” and is reproduced below:

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:		
	Acetaminophen	160.0
	Dextromethorphan Hydrochloride monohydrate	9.0 mg
20	Chlorpheniramine maleate	1.0 mg
	Phenylephrine Hydrochloride	2.5 mg
	Agave nectar	11.0 ml
	Propylene Glycol	1.74 g
	Ethanol (95%)	1.5 ml
25	Flavorants	0.05 ml
	F, D & C Red #40	5.1 mg
	Glycerin	750.0 mg
	Aspartame	23.2 mg
	Water, Purified q.s.	

(Ex. 1007 at 23:16-29.)

103. WO742 explains that the liquid of Example IX was “made by adding the active ingredients the propylene glycol, polyethylene glycol, alcohol, flavorants, and glycerin with stirring.” (Ex. 1007 at 23:30-24:2.) This solution “is added to agave nectar with stirring.” (*Id.*) The dye is then added to the solution. (*Id.*) Finally, “[p]urified water is added to volume with stirring.” (*Id.* (“q.s.” is the abbreviation for *quantum satis*, meaning to add enough of the ingredient to reach the desired result).)

104. Although WO742 expressly recognizes that agave syrups have variable viscosity (i.e., “thicker or thinner in consistency (viscosity)”), WO742 does not disclose a specific type of agave syrup that must be used or otherwise was used to

practice the “invention” disclosed therein, does not disclose a viscosity value for agave syrup or the viscosity value of the agave syrup used in any of the Examples therein, and never mentions anything relating to the viscosity of the Example formulations disclosed therein. (*See also* Ex. 1003 at ¶216 (“WO742 does not expressly disclose the viscosity (or range of viscosities) of liquid formulations of the invention”).)

VIII. CLAIM CONSTRUCTION: “AGAVE SYRUP”

105. I have been asked by counsel to opine on the meaning of “agave syrup” as a POSA reading the ’795 patent would understand it.

106. According to the ’795 patent “agave syrup” refers to a processed juice obtained from the agave sp. plant, also referred to as “processed sap” or “processed aguamiel.” (Ex. 1001 at 2:7-9.) The ’795 patent does not limit “agave syrup” to a particular type of agave syrup. The ’795 patent does expand on the meaning of syrup as a “formulation that has a flow without applied pressures.” (*Id.* at 2:9-10.) It further recognizes that “[t]he syrup can have a viscosity of between about 200 and 3500 centipoise. . . as determined by a Brookfield Viscometer at about 22 degrees.” (*Id.* at 2:12-16.)

107. Given the broad meaning put forth in the ’795 patent, a POSA would understand that agave syrup can have varying physical and chemical properties, including viscosity, depending on the type of agave plant the syrup is derived from

and the processing conditions used.

108. Agave syrup is “obtained from cooking and concentrating the juice of Agave plants.” (Ex. 1031.) I understand that Petitioner agrees that “[a] person of ordinary skill in the art would understand that agave syrup can be obtained from different species of agave and can be light or dark in color, with a thinner or thicker consistency.” (Pet. at 15.) I also understand that Dr. Crowley and Petitioner construe “agave syrup” to “encompass all liquid materials derived from any agave plant that is free flowing, irrespective of its other properties.” (*Id.*) For the purposes of this Declaration only, I agree with Dr. Crowley and Petitioner’s construction of “agave syrup,” including that such definition includes agave syrup with viscosity at least up to 2,560 cP as identified in Dr. Crowley’s and Petitioner’s cited Exhibit 1031.

IX. NON-OBVIOUSNESS OF THE ’795 PATENT

A. Agave-based Formulations with the Claimed Viscosity Are Not Obvious in light of Grounds 1 and 2

109. It is my opinion the challenged claims, 1-24, are not obvious due to there being no teaching or motivation to combine the references in Ground 1 or Ground 2 to reach the claimed viscosity ranges.

110. As Petitioner’s own evidence recognizes “[v]iscosity is one of the most significant physical chemical properties in determining the quality and acceptability

of [agave] syrup.” (Ex. 1031.)

1. Petitioner and Dr. Crowley Rely on an Incorrectly Cited Viscosity Value for Agave Syrup

111. Dr. Crowley’s opinions under Grounds 1 and 2 are premised on agave syrup having a viscosity of 212 centipoise (cP). (Ex. 1003 at ¶52 (“The viscosity of agave syrup is reported to be around 212 mPa-S, or 212 cP, which is less than that of honey or sugar cane syrup.”), ¶119 (“[a]s I previously noted at ¶ 52, a person of ordinary skill in the art would have known that agave syrup has a viscosity of around 212 centipoise”), ¶216 (agave syrup has “a viscosity around 200 centipoise”); *see also* Pet. at 31, 57.)

112. Despite expressly acknowledging his recognition that the viscosity of agave syrup is variable, Dr. Crowley provides no explanation for his arbitrarily selected single viscosity value of 212 cP. Indeed, I note this value is not disclosed in FR458, WO113, WO742, or the ’4666 Patent.

113. The only support Dr. Crowley cites to support his assertion that agave syrup has a viscosity of 212 cP is Ex. 1031, entitled “Rheology of Agave [S]yrup.” (Ex. 1003 at ¶52 (“[t]he viscosity of agave syrup is reported to be about 212 centipoise. . . . Ex. 1031, at p. 1.”).)

114. But Exhibit 1031, discloses a viscosity for agave syrup as “2.56 Pa s” (i.e., 2,560 cP) as shown below:

174 - Rheology of Agave syrup

Araceli M. Vera-Guzmán MS, Laura V. Aquino-Gonzalez, Professor Mercedes G. López Ph.D., Unidad Oaxaca, CIIDIR-IPN, Oaxaca, Oaxaca, Mexico; Biotechnology and Biochemistry, Centro de Investigación y de Estudios Avanzados, Irapuato, Guanajuato, Mexico

Agave syrup, a natural product with high sweetener capacity, is obtained from cooking and concentrating the juice of Agave plants. Viscosity is one of the most significant physical chemical properties in determining the quality and acceptability of syrup. Knowledge of the rheology of Agave syrup is therefore necessary in its production, processing, and storage. The aim of the present study was to evaluate the viscosity of Agave syrup, over five temperatures. The viscosity of 10 Agave syrup samples as well as 2 honeybee and 2 sugar cane syrup were used as references. Samples were analyzed over a range of shear rates (1.0 - 100 s⁻¹) with five temperatures (10, 20, 40, 60, and 80°C) in an Anton Park rheometer MR301. In general, the viscosity curves of all samples exhibited a Newtonian behavior. The mean viscosity values of Agave syrup, sugar cane, and honeybee were 2.56 Pa s, 6.06 Pa s, and 10.47 Pa s, respectively, at 20°C and 10 s⁻¹. The viscosity value of Agave syrup was less than the values of the references. The viscosity of Agave Syrup (8.94 - 0.16 Pa s), sugar cane syrup (74.45 - 0.23 Pa s) and honeybee (109 - 0.09 Pa s) decreased with an increase in temperature (10 - 80°C). The viscosity of samples depended on the type of syrup and the temperature of the measurement.

Wednesday, March 30, 2011 01:30 PM
[Bioactives in Natural Sweeteners \(01:30 PM - 04:50 PM\)](#)
Location: Anaheim Marriott
Room: Orange County III

KINDERFARMS Ex. 1031
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051
Page 1 of 1

UnitConverters.net

Home / Viscosity - Dynamic Conversion / Convert Pascal Second to Centipoise

Convert Pascal Second to Centipoise

Please provide values below to convert pascal second [Pa*s] to centipoise [cP], or [vice versa](#)

From: pascal second

To: centipoise

Result: 2.56 pascal second = 2560 centipoise

(Ex. 1031 at 1 (and conversion from Pa s to cP).) Thus it reports the mean viscosity in Pascal seconds rather than centipoise.

115. It is well known and understood that 1 Pascal second (Pa s) is equivalent to 1000 centipoise (cP), this is simply a trivial unit conversion. (See, e.g., <https://www.unitconverters.net/viscosity-dynamic/pascal-second-to-centipoise.htm>.) Thus, in my opinion, a person of ordinary skill in the art would have immediately understood that the viscosity value of agave syrup reported in Dr. Crowley's Ex. 1031 as 2.56 Pa s is a centipoise-scale viscosity of 2,560 cP. There is no value in Exhibit 1031 that corresponds to a viscosity of 212 cP.

116. This reported viscosity in cited Exhibit 1031 is over 10 times higher than the value of 212 cP Dr. Crowley relies on throughout his declaration (Ex. 1003 at ¶¶52, 119, 216) and Petitioner relies on in its Petition (Pet. at 31, 57).

117. As Exhibit 1031 notes, “[v]iscosity is one of the most significant physical chemical properties in determining the quality and acceptability of syrup.” (Ex. 1031 at 1.) Yet Dr. Crowley does not provide any reasoning as to why he chose to rely on a 212 cP value for the viscosity of agave syrup instead of the 2,560 cP value *actually* reported in Exhibit 1031. Nor does Dr. Crowley or Petitioner ever purport to explain why or how a POSA would have done so.

118. Although Petitioner does acknowledge that agave syrup can have varying consistencies and be “thinner or thicker” (Pet. at 15), again no reasoning is provided for the reliance on the viscosity of agave syrup being at or about 212 cP instead of any other viscosity for agave syrup, such as the 2,560 cP viscosity value reported in Ex. 1031. It is further unclear to me why Dr. Crowley and Petitioner did not address the vast differences of viscosity agave syrup may have in light of the evidence they have relied upon. In my opinion, this single error in Dr. Crowley’s opinions and the Petition, disproves any basis for obviousness because Dr. Crowley and Petitioner’s own submitted evidence disproves the sole rationale underlying the obviousness theories presented—i.e., agave syrup does not necessarily have a viscosity of 212 cP. The 2,560 cP viscosity value actually reported in Petitioner’s

Exhibit 1031 is well-above and far outside the recited viscosity of the claims and, in my opinion, could not support obviousness under Petitioner's theories (even if such assertions had been made).

119. That being said, I also note that Dr. Crowley and Petitioner never purport to identify the viscosity of any formulation it relies on within the Prior Art references or what viscosity a person of ordinary skill in the art would have believed FR458-Example 1 or WO742-Example IX would have.⁴ To the contrary, the Petition is ambiguous and non-committal on the actual or expected viscosity value for either of these examples. The Petition only asserts that “*Example 1 of FR458*, which is largely made up of agave syrup, *may have* a viscosity less than 1500 centipoise” and “*Example IX of WO742*, which consists mainly of agave syrup and other ingredients with relatively low viscosities, *may have* a viscosity of less than 1500 centipoise.” (Pet. at 31, 57 (emphasis added).) Of course, the viscosity of these example formulations that Petitioner contends are “largely” or “consists mainly of” agave syrup, will be heavily influenced by the viscosity of the agave syrup itself and a viscosity of 2,560 cP as identified in Ex. 1031 is well above 1500 cP. As such, use of that agave syrup within the examples would result in

⁴ A POSA would be aware that each example or formulation relied on would have its own distinct viscosity.

formulations that a POSA would have expected to have a viscosity of *more* than 1500 cP.

120. Rather, it appears as though Petitioner and Dr. Crowley just assume without any justification that the example formulations of FR458-Example 1 and WO742-Example IX use an agave syrup having 212 cP such that the examples “may have a viscosity of less than 1500 centipoise.” The specific viscosity value of 1500 cP does not appear in FR458, WO742, the ’4666 patent, or WO133, it only appears in the claims of the ’975 patent. In my opinion, Dr. Crowley and Petitioner are clearly relying on the patent claims as part of their obviousness arguments using hindsight, which I understand is not permitted in an obviousness analysis.

121. Further, I note that it would seem unusual to me for a POSA to choose an agave syrup of such low viscosity, such as 212 cP, if there was one available of higher viscosity, at least when preparing pharmaceutical formulations. A viscosity of 212 cP indicates to me that the agave syrup has a lower quality. (*See* Ex. 1031.) In my opinion, a POSA would plainly use a high-quality agave syrup such as an agave syrup like that reported in Ex. 1031 having a viscosity of 2,560 cP instead of an apparently watered-down low quality agave syrup with a viscosity of 212 cP. Moreover, employing a high-quality, high-viscosity agave syrup would provide a POSA with more control over the formulation process. The overall water content of the formulation is a key factor with respect to taste-masking and stability of

acetaminophen formulations. A POSA would find it beneficial to be able to control the overall water content in a formulation by using a high-viscosity and low-water agave syrup because it would minimize the need for additional artificial excipients to achieve any desired final viscosity value for the formulation since the viscosity, which can affect numerous properties and desirability of such formulations. Put simply, a formulation using an agave syrup of 212 cP could not achieve the same 2,040 cP viscosity of the commercially available Calpol acetaminophen liquid suspension (*see* Ex. 2020 at 359 (Table 1)) without adding additional thickening agents in substantial quantities to increase the viscosity and offset the watered-down low viscosity of the 212 cP agave syrup. In contrast, the amount of added water to a formulation having of an agave syrup with viscosity of 2,560 cP could be controlled to achieve Calpol's 2,040 cP viscosity without the need for additional thickeners.

2. Petitioner Fails to Address the Obvious Error in the '4666 Patent

122. Petitioner and its expert Dr. Crowley rely on the teachings of the '4666 patent to provide the viscosity limitation for both Grounds 1 and 2.

123. Both rely on the assertion that “[t]he '4666 Patent teaches controlling the viscosity of an oral liquid analgesic formulation to ensure its stability and discloses formulations with a broad range of viscosities from 100 to 3000 cP, as

measured by the Brookfield Synchro-Lectric viscometer.” (Ex. 1003 at ¶119.)

124. Dr. Crowley relies on this teaching for his analysis of claims 2, 3, and 4 which claim a viscosity of less than 1000, 750, and 600 centipoise at about 22 degrees, respectively. (Ex. 1001 at claims 2-4; Ex. 1003 at ¶132.) He states that “[b]y disclosing viscosity ranges that go as low as 100 cP and 200 cP, respectively, the ’4666 Patent and WO133 clearly teach a person of ordinary skill in the art oral liquid acetaminophen compositions with viscosities less than 1,000 cP (claim2), less than 750 cP (claim 3), or less than 600 cP (claim 4)” and therefore the ’4666 patent and WO133 make the claim limitations obvious. (Ex. 1003 at ¶¶132-33.)

125. I disagree with Dr. Crowley that a POSA would understand that the ’4666 patent teaches a viscosity range from 100 to 3000 cP.

126. The ’4666 patent’s specification provides only the following statements relating to viscosity values:

Viscosity of the product should be controlled for optimum stability. A viscosity of about 1000 to 3000 centipoise at 20° C., as measured by the Brookfield Synchro-Lectric viscometer, is the preferred range. Finished product of somewhat less thickness are capable of being stored for commercially acceptable time periods, but these are less able to withstand adverse conditions which may be encountered in storage and shipment.

(Ex. 1005 at 4:9-17.)

127. The ’4666 patent also has three dependent claims related to viscosity, each modifying the three independent claims (Claims 1, 6 and 7). The dependent

claims are reproduced below:

- 9. The syrup of claim 1 wherein the viscosity is about 1000 to 3000 centipoise at 20° C.**
- 10. The syrup of claim 6 wherein the viscosity is about 1000 to 3000 centipoise at 20° C.**
- 11. The syrup of claim 7 wherein the viscosity is about 100 to 3000 centipoise at 20° C.**

128. In accordance with the teachings of the specification (disclosing a viscosity of “about 1000 and 3000 centipoise at 20°C, as measured by a Brookfield Synchro-Lectric viscometer (Ex. 1005 at 4:9-17)), claims 9 and 10 both disclose a range of “about 1000 to 3000 centipoise.” (*Id.* at cl 9-10.) On the other hand, claim 11 discloses a range of “about 100 to 3000 centipoise.” (*Id.* at claim 11.)

129. I do not see any support for a viscosity range of “about 100 to 3000 centipoise” in the specification of the ’4666 patent. Indeed, a range of 100 to 3000 centipoise would be inconsistent with the specification which states that “[a] viscosity of about 1000 to 3000 centipoise at 20°C, as measured by the Brookfield Synchro-Lectric viscometer, is the preferred range.” (*Id.* at 4:9-17.) Although the specification states that “[f]inished product of somewhat less thickness are being capable of being stored for commercially acceptable time periods,” in my opinion a POSA would not understand “somewhat less” to mean that the preferred 1000-3000 cP range that must be “controlled for optimal stability” would extend to a product that is 90% lower in viscosity (100 cP) than the identified minimum viscosity of the

preferred range (1000 cP).

130. The specification also further explains that “[a]n important aspect of this invention is the inclusion of a major portion of water compatible material or materials that contribute to a rather heavy and uniform viscosity in the final composition.” (*Id.* at 2:41-44.) A POSA would understand that a viscosity that approaches 100 cP is characteristic of a relatively thin formulation and would not be considered a “heavy” viscosity. This again weighs against a POSA having an understanding that the ’4666 patent teaches formulations with viscosities as low as 100 cP.

131. In my further opinion, the similarity in the language of recited claims 9, 10, and 11 further demonstrate that a POSA would have immediately recognized that the “100” in claim 11 was an obvious typographical error. In my opinion, a POSA would have seen each of these three claims and, in the context of the teaching of the specification, have understood that they were each meant to recite the same consistent viscosity of “about 1000 to 3000 centipoise” (as in claims 9 and 10, and the preferred range of the specification).

132. Finally, in my opinion, a POSA would not have understood the specification of the ’4666 patent as disclosing any suggestion of a range that is a drastic, ten-fold reduction in viscosity from 1000 cP to 100 cP, for the reasons I have explained above, which further supports the conclusion that claim 11 of the ’4666

patent has an obvious typographical error.

133. Accordingly, considering the claim limitation in the context of the other claims and the specification, a POSA would have recognized that “100” is a typographical error and that the patent owner intended that claim 11 recite a viscosity range of “about 1000 to 3000 centipoise.”

3. A POSA Would Not Combine the non-overlapping viscosity ranges of the '4666 Patent and WO133

134. A POSA recognizing the error found in the '4666 patent, in my opinion, would not be motivated to combine the '4666 patent with Petitioner's other reference it relies on to meet the viscosity limitations, WO133.

135. As I previously discussed above, the '4666 patent discloses viscosities of pharmaceutical formulations from 1000 to 3000. *See* Section IX.A.2.

136. The WO133 disclosure generally describes that “acetaminophen composition generally ranges from about 200-900 centipoise, preferably from about 300-700 centipoise.” (Ex. 1006 at 10.)

137. I understand that Petitioner and Dr. Crowley contends that a POSA would have had a motivation to combine and a reasonable expectation of success in combining these disparate ranges with the formulations of FR458-Example 1 and WO742-Example IX as part of their obviousness grounds. I disagree. A POSA would have been motivated to combine non-overlapping and disparate viscosity

ranges with each other. A POSA would understand that FR458-Example 1 and WO742-Example IX are individual formulations with singular viscosity values. A POSA would immediately recognize that any single formulation with a given viscosity logically could not simultaneously satisfy both 1000-3000 cP and 200-900 cP at the same time. At best, it could only be a reasonable expectation of satisfying one or the other, but not both.

138. Further, the 200 cP minimum viscosity taught by WO133 is much thinner of a viscosity than the minimum 1000 cP viscosity taught by the '4666 patent. Based on the teachings of the '4666 patent discussed above (*see* Section IX.A.2) a POSA would be wary of such a thin formulation due to issues regarding its ability to withstand adverse conditions and remain stable. (*See* Ex. 1005 at 4:13-17.) A POSA would thus not have a reasonable expectation of success of combining these references.

B. Ground 1 Fails to Render Obvious the Claims of the '795 Patent

139. It is my opinion that the combination of FR458 with the '4666 Patent and/or WO133 does not render claims 1-24 of the '795 Patent obvious to a POSA at the time of invention. In addition to the errors I have previously described that undermine Petitioner's argument, it is also my opinion that Petitioner has failed to provide adequate motivation to combine FR458 with the '4666 Patent and/or WO133.

140. Petitioner and Dr. Crowley’s only motivation for combining the references is generic—i.e., that all three references are in the field of liquid pharmaceutical formulations for oral administration, contain analgesics, and seek to provide low glycemic index formulations that still mask the bitter taste of the active ingredient(s). (Pet. at 28-29; Ex. 1003 at ¶101.) However, this does not speak to how a POSA would be motivated to combine the three references to arrive at an agave-based suspension with the claimed viscosity as disclosed in claims 1-24 of the ’795 patent.

141. I further disagree with Petitioner and Dr. Crowley’s conclusory assertion, particularly as it pertains to agave syrup, that:

Considering that each prior art reference is in the same field of art, seeks to address similar issues, and discusses the creation of oral analgesic formulations using “old [ingredients] with each performing the same function it had been known to perform,” a person of ordinary skill in the art would be motivated to combine these teachings and would have a reasonable expectation of success in combining these teachings.

(See Pet. at 29; Ex. 1003 at ¶119.)

142. While agave syrup may be known as a sweetener for food products, I disagree that agave syrup is a well-known “old ingredient” performing a function it was known to perform in the context of an oral pharmaceutical formulation with a

specified and desired viscosity. In my opinion, if agave syrup was so well-established in the field, Petitioner and Dr. Crowley would not have made so glaring of an error of agave syrup having a viscosity (212 cP) that is an order of magnitude less than the actual reported value in the cited Exhibit 1031 (2.560 cP). In my opinion, this error belies any assertion that agave syrup is simply a well-known and well-established ingredient for pharmaceutical formulations. That is, if agave syrup was such a well-known ingredient for liquid pharmaceutical formulations certainly Dr. Crowley would have recognized that he was relying on a viscosity that is not even what is reported in his own cited Exhibit 1031.

143. Additionally, Dr. Crowley's Exhibit 1031 itself demonstrates that agave syrups have different "quality and acceptability" and that "viscosity is one of the most significant physical chemical properties in determining the quality and acceptability of [agave] syrup." (Ex. 1031.) Dr. Crowley also recognized that "agave syrup is obtained from the agave plant by extracting its juice and processing it into a syrup, and this syrup can be light or dark in color, thicker or thinner in consistency (viscosity)." (Ex. 1003 at ¶68.) Consistent with this, it was known that "[t]he variability of production methods, kind of agave, growing agave's region, and part of the plant used in the production process (sap, leaves or pine), generates a wide range of products sold under the name of agave syrup." (Ex. 2013 at 50-51.) Accordingly, it was also known that different agave syrups have "[a] *wide variability*

of physicochemical quality parameters.” (*Id.* at 56.) It was also recognized in “[f]urther analysis of a wide range of [agave] syrups . . . **are needed** to get more information for a deeper characterization of agave syrups.” (*Id.* at 50.) In my opinion, the broad variability of agave syrup, particularly coupled with Petitioner’s and Dr. Crowley’s erroneously cited viscosity from Exhibit 1031, further demonstrates that agave syrups are not the same sort of a singular uniform ingredient that is well-known for use in oral formulations.

144. While other standard components of pharmaceutical formulations can be found in textbooks and standard pharmaceutical references, Dr. Crowley has not identified “agave syrup” within any such references. For instance, Dr. Crowley’s cited “Handbook of Pharmaceutical Excipients” has no entry for agave syrup. (*See* Ex. 1029 at 14 (no entry for agave syrup).) Similarly, a there is no United States Pharmacopeia (USP) monograph for agave, let alone agave syrup. (*See* Ex. 2016.) Agave syrup is also nowhere disclosed in the FDA index of generally recognized as safe (GRAS) ingredients. (*See* Ex. 2015.) Indeed, in my experience, agave syrup is not a typical inactive ingredient that was used in pharmaceuticals as of 2021, including in over-the-counter pharmaceutical products.

145. Indeed, Petitioner and Dr. Crowley were only able to muster two instances of the use of agave syrup in an oral pharmaceutical formulation—FR458 and WO742. But neither of those references discloses the type of agave syrup that

was used, the viscosity of the agave syrup, or the viscosity of any of the formulations taught or disclosed within them.

146. Thus, in my opinion, it is abundantly clear that agave syrup is not merely an “old ingredient” that was well-known and performing the same well-known function that it performs in the formulations claimed in the ’795 patent. Again, if agave syrup was a clearly established and well-known ingredient, then Dr. Crowley should have recognized his erroneous citation to the viscosity of agave syrup in Ex. 1031 and would not have wrongly asserted that “a person of ordinary skill in the art would have known that agave syrup has a viscosity of around 212 centipoise” when his own cited Exhibit 1031 reports a viscosity of 2,560 cP. (Ex. 1003 at ¶119.)

147. With respect to the viscosity limitation of claim 1, neither the Petitioner nor Dr. Crowley ever identify any motivation to combine any specific aspects of FR458 with any of the specific aspects of either the ’4666 patent and/or WO133, instead merely relying on their stated motivation that the entirety of these references can be combined in any way because they are in the same general field. Nevertheless, I understand that Petitioner and Dr. Crowley identify: (1) the erroneous assertion that agave syrup has a viscosity of 212 cP; (2) FR458-Example 1; and (3) the viscosity ranges of the ’4666 patent (1000-3000 cP) and WO133 (200-900 cP). (*See* Pet. at 31-32; Ex. 1003 at ¶119.) Neither Petitioner nor Dr. Crowley

purport to identify the viscosity of FR458-Example 1 or the type and viscosity of the agave syrup within it.

148. Further, based on Petitioner's evidence, a POSA would not have been motivated to apply these viscosities to the examples in FR458. Petitioner's expert, Dr. Crowley, states that "suspensions having a viscosity in the range of 20 to 150 cP are considered readily pourable." (Ex. 1003 at ¶59 (citing Ex. 1014 at pp.1489-1490).) This obviously well below and outside the 1000-3000 cP range of the '4666 patent and the 200-900 cP range of WO133. Dr. Crowley also opines that "higher viscosity is generally not desirable." (Ex. 1003 at ¶59.) If this is the case, a POSA would not have a motivation to combine FR458 with the viscosity ranges of the '4666 patent and/or WO133, both of which teach viscosities greater than 150 cP and Dr. Crowley's own statements thus reflect a teaching away from any such combination.

149. Indeed, this is even more the case, when you consider the fact that Petitioner and its expert rely on the inherent viscosity of agave being 212 cP. If an agave syrup with 212 cP was used in FR458-Example 1, a POSA would immediately recognize it would not fall within the viscosities disclosed by the '4666 patent (1000-3000 cP) or WO133 (200-900 cP), discounting any motivation to make such a combination or any reasonable expectation of success in doing so. To the contrary, a POSA would recognize that FR458-Example 1 includes a large amount of water

(at least ~50% by volume and ~45% by mass) such that it would be the most predominant component of the formulation.

150. A POSA would have understood that the use an agave syrup with a viscosity 212 cP with FR458-Example 1 (and the other ingredients therein) would be watered-down by such a large amount of added water that the POSA would expect the overall formulation to have a viscosity closer to water than the starting viscosity of the agave syrup—i.e., certainly well below 200 cP and more likely than not below 100 cP.⁵ Such a formulation would be a formulation that Dr. Crowley has recognized as being “readily pourable” (Ex. 1003 at ¶52 (“a viscosity in the range of 20 to 150 cP are considered readily pourable”).) Thus, in my opinion, a POSA would not have had any motivation or reasonable expectation of success in combining an agave syrup with viscosity of 212 cP in FR458-Example 1 with the viscosity ranges 1000-3000 cP of the ’4666 patent or 200-900 cP of WO133 because the expected viscosity of such a formulation would fall well below and outside either of these ranges. I note that Dr. Crowley proposed no modifications to FR458-Example 1 and never addresses why there would be any motivation to combine FR458 with the ’4666 patent and/or WO133 if agave syrup has the viscosity reported in Ex. 1031 of

⁵ That being said, it is my opinion that agave syrup has a much higher viscosity than 212 cP as detailed by Ex. 1031.

2,560 cP.

151. Beyond that, in my opinion, a POSA would have understood that the '4666 teaches that the formulation should include at least 50-75% by weight of a water compatible bodying agent, which is ideally a polyhydric alcohol and teaches against using large amounts of sugars. (Ex. 1005 at 2:41-56.) In particular, the '4666 patent teaches using large amounts of glycerol, sorbitol, mannitol, and propylene glycols as the bodying agent. (*Id.* at 2:52-54.) As discussed in the '4666 patent, sugars should be merely an “incidental amount” of the water compatible bodying agent. (*Id.* at 2:59-65.)

152. Dr. Crowley and Petitioner provide no reasoning as to why a POSA would be motivated to combine a formulation containing only an “incidental amount” of sugar, as taught by the '4666 patent, with the FR458-Example 1 formulation containing roughly 45% by mass agave syrup (and its constituent sugars).

153. In sum, it is my opinion that Petitioner and Dr. Crowley's Ground 1 fails to demonstrate that any claims of the '795 patent would have been obvious.

1. Ground 1 Also Does Not Render the Dependent Claims as Obvious

154. For similar reasons, it is my opinion that Ground 1 also does not render the dependent claims as obvious.

2. Dependent Claims 2-4, 15, & 19

155. Claims 2-4 and 19 of the '795 patent narrow the viscosity range of independent claims 1 and 18 to being “less than 1000 centipoise,” “less than 750 centipoise,” or “less than 600 centipoise.” (Ex. 1001 at 5:42-50.) Claim 15 further narrows the viscosity range of independent claim 7 to “a viscosity from about 1500 centipoise to about 400 centipoise.” (*Id.* at 6:24-29.)

156. For all the reasons discussed above, as well as in Sections IX.A-IX.B, a POSA would not be motivated to combine FR458 with the '4666 patent and/or WO133 to meet these narrower viscosity limitations.

3. Dependent Claims 5, 6, & 8

157. Claims 5, 6, and 8 further specify the concentration of the acetaminophen within the claimed formulations as being “0.01 to 2 grams...per 100 mL,” “0.01 to 1 grams...per 100 mL,” and “between 0.01% to 2% of the formulation by weight.” (Ex. 1001 at 5:51-56, 6:6-8.)

158. Example 1 of FR458 relied on by Petitioner includes 2.5 grams of acetaminophen (paracetamol). (Ex. 1004 at 25.) FR458 teaches more generally that the active ingredient concentration can span a wide range: “the API can be between 0.01 to about 90% of the formulation.” (Ex. 1004 at p.29, lns.20-26.) WO133 teaches a concentration of an active “up to about 10% by weight.” (Ex. 1006 at 2:16-19.) Further the '4666 patent teaches “50 to 400 mg of ibuprofen per 5 mL of syrup.”

(Ex. 1005 at 2:4-6.) This corresponds to 1 gram to 8 grams of ibuprofen per 100 mL. In my opinion, these ranges are so broad that they would not necessarily render the much narrower concentration ranges of claims 5, 6, and 8 obvious.

159. This additional limitation also does not impact the fact that the claims still require the viscosity limitations found in independent Claims 1 and 7. Yet, Dr. Crowley does not address how the variability of acetaminophen concentration would impact the viscosity of any formulation, let alone that of FR458 Example 1. Acetaminophen takes the form of insoluble particles that need to be suspended in the syrup. Thus, the concentration of the acetaminophen within the syrup could affect the overall viscosity of the formulation, depending on how much acetaminophen is present and particularly at the upper ends of the ranges relied on by Dr. Crowley (i.e., up to 10% or up to 90% or up to 8 grams/100 mL). Accordingly, there would be no motivation or expectation of success in combining these references to achieve the claimed acetaminophen ranges at the claimed viscosity from the broad generically disclosed acetaminophen concentrations relied on by Dr. Crowley.

4. Dependent Claim 9

160. Claim 9 requires that the amount of diluent is “about 5%” of the formulation by weight. (Ex. 1001 at 6:9-11.) FR458 Example 1 discloses a formulation of over at least 45% water by weight. (*See above*, ¶149.) This is far

greater than the 5% diluent claimed by the '795 patent.

161. In my review of the Petition and Dr. Crowley's declaration, there is no explanation as to why a POSA would be motivated to implement a ten-fold decrease in the amount of water in FR458-Example 1. I also note there is no explanation provided by Petitioner or Dr. Crowley for how the change in the amount of diluent would affect the viscosity of Example 1 of FR458 or if the resulting formulation would meet the claimed viscosity limitation. Based on this, I believe there is no motivation or expectation of success in combining these references to achieve the claimed diluent concentration while maintaining the claimed viscosity based on the references of Ground 1.

5. Dependent Claims 13 & 24

162. Claims 13 and 24 include an additional limitation that "the agave syrup is about 95% of the formulation by weight." (Ex. 1001 at 6:19-21, 57-58.)

163. The agave syrup concentration of FR458-Example 1 would be around or somewhat less than 45% of the formulation by weight. (See Ex. 1004 at p.25, ln.198.)

164. Petitioner and its expert provide no reasoning or motivation within the references of Ground 1 as to why one would increase the concentration of agave by over two-fold, nor does it discuss how this would affect the viscosity of the formulation, which is still required by the claims. Based on this, I believe there is

no motivation or expectation of success in combining these references to achieve the claimed agave syrup concentration while maintaining the claimed viscosity based on the references of Ground 1.

C. Ground 2 Fails to Render Obvious the Claims of the '795 Patent

165. As discussed above, although WO742 discloses an acetaminophen pharmaceutical formulation containing agave syrup, as Dr. Crowley acknowledges in his declaration WO472 contains no details related to the viscosity of liquid pharmaceutical formulations. (Ex. 1003 at ¶216 (“WO742 does not expressly disclose the viscosity (or range of viscosities) of liquid formulations of the invention”).) WO742 also does not disclose the type of agave nectar it utilizes or its viscosity, neither generally nor in specific relation to WO742-Example IX.

166. I incorporate all of my reasonings for Ground 1 here as to why agave syrup is not simply a well-known ingredient that is being used in a manner for which it is well established, contrary to Petitioner and Dr. Crowley’s statements and why Petitioner’s errors regarding the viscosity of agave and the teachings of the ’4666 patent weigh against a finding of obviousness. (*See generally above*, ¶¶111-138.)

167. For the sake of clarity, as with Ground 1, I note that neither Petitioner nor Dr. Crowley have addressed how the references in Ground 2 would satisfy the independent claims if utilizing a high-quality agave syrup with a viscosity of 2,560 cP found in Ex. 1031. Nor does either make any argument regarding the motivation

to combine such references with a reasonable success under such circumstances.

168. The Petitioner and its expert also do not provide any evidence as to what a POSA would have understood the viscosity of WO742-Example IX to be. To the extent that one relied on Petitioner's asserted viscosity of agave syrup of 212 cP or Dr. Crowley's assertion under this Ground that a POSA would "know that agave syrup can have a viscosity of around 200 centipoise," a POSA would have understood and immediately recognized that such a formulation of WO742-Example IX would result in formulation with a much lower viscosity than the initial viscosity of the agave syrup—i.e., it would be less than 200 cP and at most around ~100 cP.

169. This is because WO742-Example IX contains 10% by volume ethanol (*see* Ex. 1007 at 23:17-24:2), and a POSA would have understood that the ethanol would have a considerable impact on the formulation's viscosity by causing it to thin and reduce the viscosity imparted by the agave syrup. A POSA would have further understood that the overall viscosity of the formulation would be further reduced by the water added to the formulation to reach the desired 15 mL dose volume. (*Id.*) The viscosity of the formulation would also be lowered due to the formulation's inclusion of propylene glycol. (*See id.* at 23:23.) The viscosity of propylene glycol (58.1 cP) is much lower than Petitioner's identified inherent viscosity of agave (212 cP) and it would therefore cause the overall formulation to be thinner than the agave syrup. (*See* Ex. 1029 at 592.) That is, the overall composition of WO742-Example

IX has a substantial amount of components with viscosities less than agave syrup that would result in the overall formulation's viscosity being well below the starting viscosity of the agave syrup (i.e., either Petitioner's 212 cP or Dr. Crowley's "about 200 cP"). A POSA would thus understand the inclusion of all of these additives would decrease the viscosity of the formulation well below that of the 212 or about 200 viscosity proposed agave syrup by Petitioner and Dr. Crowley. (*See* Ex. 2022; Ex. 1029 at 592 (Table V).)

170. In fact, a POSA would be aware that the viscosity of sugars and polyols have non-linear changes in viscosity when solvents such as ethanol or water are added to them. For instance, adding water to an aqueous solution of 83% glycerin to 70% glycerin changes the viscosity from 111.0 cP to 22.94 cP, a decrease of approximately 88 cP. (Ex. 1029 at 284 (Table VI).) Whereas, further addition of water to an aqueous solution of 70% glycerin to 60% glycerin only further decreases the viscosity by 12 cP. As such, a POSA would reasonably understand that a similar trend with respect to the decrease in viscosity of aqueous solutions of sugar and polyols would show similar trends in the drop in viscosity as additional water is added (and vice versa). (*See, e.g.*, Ex. 2022.)

171. A POSA therefore would have had no motivation, nor a reasonable expectation of success, of combining an agave syrup with a viscosity of 212 cP or about 200 cP with the remaining ingredients as taught by WO742-Example IX to

achieve a formulation with a viscosity in the range of either the '4666 patent (1000-3000 cP) or WO133 (200-900 cP). Because of the known and expected thinning caused by the other ingredients—e.g., the ethanol and added water—a POSA to understand the viscosity of WO742-Example IX using an agave syrup of 200 cP would not satisfy these ranges. Moreover, even if there was any motivation to combine WO742-Example IX with the viscosity ranges of the '4666 patent or WO133, any such motivation would necessarily indicate to a POSA *not* to use an agave syrup with about 200 cP, contrary to what Petitioner and Dr. Crowley have relied on.

172. Accordingly, it is my opinion that Ground 2 cannot establish obviousness of any of claims 1-17 of the '795 patent.

1. Ground 2 Also Does Not Render the Dependent Claims as Obvious

173. For similar reasons, it is my opinion that Ground 2 also does not render the dependent claims as obvious.

2. Dependent Claims 2-4 & 15

174. Claims 2-4 of the '795 patent narrow the viscosity range of independent claim 1 to being “less than 1000 centipoise,” “less than 750 centipoise,” or “less than 600 centipoise.” (Ex. 1001 at 5:42-50.) Claim 15 further narrows the viscosity range of independent claim 7 to “a viscosity from about 1500 centipoise to about 400

centipoise.” (*Id.* at 6:24-29.) For the same reasons discussed above regarding Ground 1, a POSA would not be motivated to combine WO742 with the ’4666 patent and/or WO133 to meet these narrower viscosity limitations. (*See above* at ¶156)

3. Dependent Claims 5-6

175. Claims 5 & 6 further specify the concentration of the acetaminophen within the claimed formulations as being “0.01 to 2 grams...per 100 mL” and “0.01 to 1 grams...per 100 mL.” (Ex. 1001 at 5:51-56.) I note that Petitioner further contends that the concentration of acetaminophen in WO742-Example IX is “1 mg per 100 mL.” (Pet. at 61.) However, I find that this is outside the scope of these claims as “1 mg per 100 mL” is equivalent to 0.001 g per 100 mL, which is below the floor set in claims 5 and 6.

176. Petitioner’s reliance on WO133’s broad teaching of a concentration of an active “up to about 10% by weight” is such a broad range that, in my opinion, does not render the much narrowed recited limitations obvious for the same reason as I set for the above in Ground 1. (*See above*, ¶¶158-159.)

177. This additional limitation does not impact the fact that the claims still require the viscosity limitations found in independent claim 1. Yet, Petitioner and Dr. Crowley again do not address how the variability of acetaminophen concentration would impact the viscosity of any formulation, let alone how it would impact the viscosity of WO742-Example IX. As previously discussed,

acetaminophen takes the form of insoluble particles that need to be suspended in the syrup. Thus, the concentration of the acetaminophen within the syrup would affect the overall viscosity of the formulation, particularly at the upper ends of the up to 10% by weight range asserted by Petitioner. There would be no motivation or expectation of success in combining these references to achieve the claimed acetaminophen ranges at the claimed viscosity.

4. Dependent Claim 9

178. Claim 9 requires that the amount of diluent is “about 5%” of the formulation by weight. (Ex. 1001 at 6:9-11.) WO742-Example IX has a final volume of 15 mL. (Ex. 1007 at 23:17-24:2.) I note that the Petition and Dr. Crowley do not explain how WO742-Example IX would need to be altered to ensure it contains about 5% diluent (or water). Indeed, there is no reasoning provided as to why one would be motivated to alter the amount of diluent in WO742-Example IX when the formulation volume is already identified. I also note there is no explanation provided by Petitioner or Dr. Crowley for how the change in the amount of diluent would affect the viscosity of Example IX of WO742 or if the resulting formulation would meet the claimed viscosity limitation. Based on this, I believe there is no motivation or expectation of success in combining these references to achieve the claimed diluent concentration while maintaining the claimed viscosity based on the references of Ground 2.

5. Dependent Claim 13

179. Claims 13 includes an additional limitation that “the agave syrup is about 95% of the formulation by weight.” (Ex. 1001 at 6:19-21.) Petitioner and its expert provide no reasoning or motivation within the references of Ground 2 as to why one would increase the concentration of agave syrup to 95% in WO742-Example IX, nor does it discuss how this would affect the viscosity of the formulation, which is still required by the claims. Based on this, I believe there is no motivation or expectation of success in combining these references to achieve the claimed agave syrup concentration while maintaining the claimed viscosity based on the references of Ground 2.

D. It Is Unnecessary to Address Petitioner’s “Alternative” Ground 3

180. I understand Petitioner has asserted the claim terms “palatable,” “stable,” and “consisting essentially of” are indefinite purely as an alternative to Grounds 1 and 2. (Pet. at 68-69; Inst. Dec. at 18 (“Essentially, Petitioner argues that if the prior art fails to teach the limitations in question, then they would necessarily be indefinite as “a person of ordinary skill in the art would not understand’ their meaning.”); Ex. 1003 at 68 (“In the alternative, Claims 1 through 24 are Indefinite . . .”).) I understand that Board recognized that “this ground of challenge is presented ‘[i]n the alternative,’ because although Petitioner asserts that a person of ordinary skill in the art can apply the plain meanings to these terms, which are proposed in

the construction section of the Petition, Patent Owner may argue that the cited prior art references do not teach one or more of these limitations.” (Inst. Dec. at 17 (citing Pet. at 68-69).)

181. None of my opinions trigger these conditions, hence I understand it is unnecessary to respond to Petitioner’s Ground 3.

182. For completeness, however, I further understand that the Board addressed Petitioner’s Ground 3 stating “we do not find the identified limitations to be indefinite” and “we are not persuaded by Petitioner’s arguments that the identified limitations are indefinite.” (Inst. Dec. at 18.)

X. CONCLUSION

183. Based on the foregoing, it is my opinion that neither Ground 1 or Ground 2 has established that any claims of the ’795 patent would have been obvious.

XI. CERTIFICATION

184. 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 this proceeding. If required, I will appear for cross-examination at the appropriate time. I reserve the right to offer opinions relevant to the invalidity of the challenged claims and/or offer testimony in support of this Declaration.

185. I hereby declare that all statements made herein of my own knowledge are true and that all statements are 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 18 U.S.C. § 1001.

Dated: June 14, 2024



Dr. Cory J. Berkland

APPENDIX A

Cory J Berkland

Mark and Becky Ruhmann Levin Professor
Department of Biomedical Engineering
Department of Chemistry
Washington University in Saint Louis

Office: (785)-864-1455
300G Whitaker Hall
1 Brookings Drive
Saint Louis, MO 63141
coryb@wustl.edu

Academic Positions

Professor, Biomedical Engineering, Washington University in Saint Louis	2023-present
Professor, Chemistry, Washington University in Saint Louis	2023-present
Solon E. Summerfield Professor, Pharmaceutical Chemistry, The University of Kansas	2015–2023
Solon E. Summerfield Professor, Chemical & Petroleum Eng., The University of Kansas	2015–2023
Associate Professor, Pharmaceutical Chemistry, The University of Kansas	2012–2015
Associate Professor, Chemical & Petroleum Engineering, The University of Kansas	2012–2015
Assistant Professor, Pharmaceutical Chemistry, The University of Kansas	2004–2009
Assistant Professor, Chemical & Petroleum Engineering, The University of Kansas	2004–2009

Education and Professional Training

Sabbatical, Sofinnova Ventures, Menlo Park, CA	2014
Ph.D. Chemical and Biomolecular Engineering, University of Illinois, Urbana, IL	May 2003
M.S. Chemical Engineering, University of Illinois, Urbana, IL	May 2001
B.S. Chemical Engineering, Iowa State University, Ames, IA	December 1998

Professional Experience

Co-founder and President, Axioforce, Saint Louis, MO	2022-present
Co-founder and Chief Executive Officer, Kinimmune, Saint Louis, MO	2020-present
Co-founder, Chairman, and Chief Executive Officer, Bond Biosciences, New York, NY	2020-2023
Co-founder and Chief Scientific Officer, Bond Biosciences, New York City, NY	2015-present
Co-founder and Chairman of the Board, Orion BioScience, Omaha, NE	2013-present
Co-founder and Chief Technology Officer, Savara Pharmaceuticals, Austin, TX	2008-2014
Co-founder and Chief Scientific Officer, Orbis Biosciences, Lenexa, KS	2007-2020

Awards

Bellows Scholar, The University of Kansas, Lawrence, KS	2018
National Academy of Inventors, Washington DC	2017
Bellows Scholar, The University of Kansas, Lawrence, KS	2016
Fellow of the American Institute of Medical and Biological Engineering	2015
Bellows Scholar, The University of Kansas, Lawrence, KS	2014
Jim Baxendale Commercialization Award, The University of Kansas, Lawrence, KS	2014
Iowa State University Professional Progress in Engineering Award, Ames, IA	2013
Leading Light Award, The University of Kansas, Lawrence, KS	2013
Miller Scholar, The University of Kansas, Lawrence, KS	2013
Controlled Release Society Young Investigator Award, Quebec City, Canada	2012
Coulter Foundation Fellow, The Coulter Foundation	2012
University Scholarly Achievement Award, The University of Kansas, Lawrence, KS	2012
Nagai Foundation Distinguished Lectureship, Annual DDS Conference, Shizuoka, Japan	2011
Miller Scholar, The University of Kansas, Lawrence, KS	2011
Kemper Fellowship for Teaching Excellence, The University of Kansas, Lawrence, KS	2010
Featured in Science Magazine Online, "The Entrepreneurial Bug"	2009
Bellows Scholar, The University of Kansas, Lawrence, KS	2008
Coulter Translational Research Award, The Coulter Foundation	2008

Teaching Achievement Recognition, Center for Teaching Excellence, Lawrence, KS	2007
Outstanding Reviewer for the Journal of Pharmaceutical Sciences	2007
Miller Scholar, The University of Kansas, Lawrence, KS	2006
Outstanding Reviewer for the Journal of Pharmaceutical Sciences	2005
Genencor Outstanding Paper Award, Controlled Release Society, Honolulu, HI	2004
Best Presentation, Chemical and Biomolecular Engineering Symposium, Urbana, IL	2003
Graduate College Travel Award, Urbana, IL	2003
Highlights of Student Posters Award, Controlled Release Society, Seoul, Korea	2002
Whitaker Award, American Chemical Society, Particles meeting, Orlando, FL	2002
Featured Technology, University of Illinois Technology Showcase, Urbana, IL	2001

Publications

1. Miller JD, Cabarkapa D, Miller AJ, Frazer LL, Templin TN, Eliason TD, Garretson SK, Fry AC, Berkland CJ (2023) Novel 3D Force Sensors for a Cost-Effective 3D Force Plate for Biomechanical Analysis, *Sensors*, 23(9):4437
2. Johnson SN, Brucks SD, Apley KD, Farrell MP, Berkland CJ (2023) Multivalent Scaffolds to Promote B cell Tolerance, *Molecular Pharmaceutics*, *in press*
3. Firdessa-Fite R, Johnson SN, Leon MA, Sestak JO, Berkland C, Creusot RJ (2023) Soluble antigen arrays improve the efficacy and safety of peptide-based tolerogenic immunotherapy, *in press*
4. Joaquina C Baranda, Ghulam Rehman Mohyuddin, Andrés M Bur, Yelizaveta Shnayder, Kyle R Sweeney, Kiran Kakarala, Megan Prouty, Harsh Pathak, Rajni Puri, Amrita Mitra, Rashna Madan, M Laird Forrest, Aric Huang, Scott Weir, Andrew K Godwin, Nabil A Alhakamy, J Daniel Griffin, Cory J Berkland (2023) A window of opportunity trial evaluating intratumoral injection of Copaxone® in patients with percutaneously accessible tumors, *Translational Medicine Communications*, 8(1)
5. Aparna Raghavachar Chakravarti, Chad E Groer, Huan Gong, Vivian Yudistyra, Marcus Laird Forrest, and Cory J Berkland (2023) Design of a Tumor Binding GMCSF as Intratumoral Immunotherapy of Solid Tumors, *Molecular Pharmaceutics*, 20(4):1975-1989
6. Aric Huang, Suresh E Kurhade, Patrick Ross, Kyle D Apley, Jonathan Daniel Griffin, Cory J Berkland, Mark P Farrell (2022) Disrupting N-Glycosylation Using Type I Mannosidase Inhibitors Alters B-Cell Receptor Signaling, *ACS Pharmacology and Translational Sciences*, 5(11):1062-1069
7. Aric Huang, Chad Groer, Ruolin Lu, M Laird Forrest, Jonathan Daniel Griffin, Cory J Berkland (2022) Glatiramer Acetate Complexed with CpG as Intratumoral Immunotherapy in Combination with Anti-PD-1, *Molecular Pharmaceutics*, 19(11):4357-4369
8. Fah Chueahongthong, Singkome Tima, Sawitree Chiampanichayaku, Pornngarm Dejkriengkraikul, Siriporn Okonogi, Mathurada Sasarom, Soraya Rodwattanagul, Cory Berkland, Songyot Anuchapreeda (2022) Doxorubicin-Loaded Polymeric Micelles Conjugated with CKR- and EVQ-FLT3 Peptides for Cytotoxicity in Leukemic Stem Cells, *Pharmaceutics*, 14(10)
9. Aric Huang, Wei Jin, Ahmed S. Fahad, Brooklyn K. Mussman, Grazia Paola Nicchia, Bharat Madan, Matheus Oliveira de Souza, J. Daniel Griffin, Jeffrey L. Bennett, Antonio Frigeri, Cory J. Berkland, and Brandon J. DeKosky (2022) Strategies to Screen Anti-AQP4 Antibodies from Yeast Surface Display Libraries, *Antibodies*, 11(39)
10. D Even, CJ Berkland (2022) Selectivity of dehydrogenative silicone-oxygen bond formation in diphenylsilane by base and base-activated catalysts, *International Journal of Chemical Kinetics*, 54(8):478-487

11. Anna Wilson, Leslie Laguna, Lansten Yew, Kerry Kao, Kathryn Bauguess, Jiaying Wang, Sofia de la O, Grant Romme, William Gilbert, Ana Rita C Morais, Jian Qian, Cory J Berkland, David R Corbin, Mark B Shiflett (2022) Sorbents for treatment of hereditary hemochromatosis, *Medicinal Chemistry Research*, 31(1):85-93
12. Jonathan D Miller, Dimitrije Cabarkapa, Matthew J Hermes, Andrew C Fry, Cory J Berkland (2022) Soft Magnetic Composites as Quantitative 3D Compression Sensors for Wearable Technology, *Advanced Materials Technologies*, 7(3):2100784
13. J Qian, NP Wiederhold, T Patterson, H Patterson, CJ Berkland (2021) Polymeric Iron Chelator with Enhanced Iron Affinity as a Broad-Spectrum Antifungal Agent, *ACS Applied Polymer Materials* 3(12):6034-6039
14. Kyle D Apley, Amy D Laffin, Stephanie N Johnson, Noora Batrash, J Daniel Griffin, Cory J Berkland, Brandon J DeKosky (2021) Optimized Production of Fc Fusion Proteins by Sortase Enzymatic Ligation, *Industrial & Engineering Chemistry Research*, 60(47):16839-16853
15. Chueahongthong F, Tima S, Chiampanichayakul S, Berkland C, Anuchapreeda S. (2021) Co-Treatments of Edible Curcumin from Turmeric Rhizomes and Chemotherapeutic Drugs on Cytotoxicity and FLT3 Protein Expression in Leukemic Stem Cells, *Molecules*, 26(19):5785
16. Bryce J Stottlemire, Aparna Chakravarti, Jonathan Whitlow, Cory J Berkland, Mei He (2021) Remote-Controlled 3D Porous Magnetic Interface toward High-Throughput Dynamic 3D Cell Culture, *ACS Biomaterials Science & Engineering*, 7(9):4535-4544
17. Pressnall MM, Huang A, Groer CE, Huayamares SG, Laird Forrest M, Berkland CJ. (2021) Glatiramer acetate enhances tumor retention and innate activation of immunostimulants, *International Journal of Pharmaceutics*, 605:120812
18. Lou H, Berkland C, Hageman MJ. (2021) Simulating particle movement inside subcutaneous injection site simulator (SCISSOR) using Monte-Carlo method, *International Journal of Pharmaceutics*, 605:120824
19. Gelareh Samandi, Vineet Gupta, Neethu Mohan, Peter McHugh, Cory Berkland, Michael Detamore, Stefan Lohfeld (2021) Polymer-coated microparticle scaffolds engineered for potential use in musculoskeletal tissue regeneration, *Biomedical Materials*, 16(4)
20. Bryce J Stottlemire, Jonathan D Miller, Jonathan Whitlow, Sebastian G Huayamares, Prajnaparamita Dhar, Mei He, Cory J Berkland (2021) Remote Sensing and Remote Actuation via Silicone-Magnetic Nanorod Composites, *Advanced Materials Technologies*, 6:6:2001099
21. J Qian and CJ Berkland (2021) Drug Release Kinetics from Nondegradable Hydrophobic Polymers Can Be Modulated and Predicted by the Glass Transition Temperature, *Advanced Healthcare Materials*, 10(12):e2100015
22. NA Alhakamy, DT Curiel, CJ Berkland (2021) The era of gene therapy: from preclinical development to clinical application, *Drug Discovery Today*, 26(7):1602-1619
23. Rebuma Firdessa-Fite, Stephanie N Johnson, Martin A Leon, Mohsen Khosravi-Maharlooei, Rocky L Baker, Joshua O Sestak, Cory Berkland, Remi J Creusot (2021) Soluble Antigen Arrays Efficiently Deliver Peptides and Arrest Spontaneous Autoimmune Diabetes, *Diabetes*, 70(6):1334-1346
24. Sawalee Saosathan, Jalernsri Khounvong, Methee Rungrojsakul, Trinnakorn Katekunlaphan, Singkome Tima, Sawitree Chiampanichayakul, Cory Berkland, Songyot Anuchapreeda (2021) Costunolide and parthenolide from Champi Sirindhorn (*Magnolia sirindhorniae*) inhibit leukemic cell proliferation in K562 and molt-4 cell lines, *Natural Product Research*, 35(6):988-992

25. JK Ruffalo, JD Miller, CJ Berkland (2021) Compression sensors constructed from ferromagnetic particles embedded within soft materials, *MRS Communications*, 11:94-99
26. Jimmy Yuanxi Song, J Daniel Griffin, Nicholas R Larson, Matthew A Christopher, C Russell Middaugh, Cory J Berkland (2021) Synthetic Cationic Autoantigen Mimics Glatiramer Acetate Persistence at the Site of Injection and is Efficacious Against EAE, *Frontiers in Immunology*, 11:3525
27. J Daniel Griffin, Sebastian G Huayamares, Towne R Walston, Jimmy Y Song, Michael Shao, Alexander R Sedlacek, Deanna L Diaz, Aparna R Chakravarti, Cory J Berkland (2020) Brain Homogenate Decoys for Antigen-Specific Cell Amplification, *ACS Applied Bio Materials*, 4(1):387-391
28. Apley KD, Griffin JD, Johnson SN, Berkland CJ, DeKosky BJ (2020) Tetrameric Fluorescent Antigen Arrays for Single-Step Identification of Antigen-Specific B Cells, *Journal of Visualized Experiments*, 164
29. Andrews BT, Barbay S, Tsau S, Berkland C, Townsend J, Detamore M, Tucheck C, Nudo RJ (2020) Manifestations of Apprehension and Anxiety in a Sprague Dawley Cranial Defect Model, *Journal of Craniofacial Surgery*, 31(8):2364-2367
30. SN Johnson, JD Griffin, C Hulbert, BJ DeKosky, JW Thomas, CJ Berkland (2020) Multimeric insulin desensitizes insulin-specific B cells, *ACS Applied Bio Materials*, 3(9):6319-6330
31. Groer C, Zhang T, Lu R, Cai S, Mull D, Huang A, Forrest M, Berkland C, Aires D, Forrest ML (2020) Intratumoral Cancer Chemotherapy with a Carrier-Based Immunogenic Cell-Death Eliciting Platinum (IV) Agent, *Molecular Pharmaceutics*, 17(11):4334-4345
32. Huayamares SG, Song JY, Huang A, Crowl SR, Groer CE, Forrest ML, Berkland CJ (2020) Constructing a Biomaterial to Simulate Extracellular Drug Transport in Solid Tumors, *Macromolecular Biosciences*, 20(12):e2000251
33. Christopher MA, Johnson SN, Griffin JD, Berkland CJ (2020) Autoantigen Tetramer Silences Autoreactive B Cell Populations, *Molecular Pharmaceutics*, 17(11):4201-4211
34. Huang A, Pressnall MM, Lu R, Huayamares SG, Griffin JD, Groer C, DeKosky BJ, Forrest ML, Berkland CJ (2020) Human intratumoral therapy: Linking drug properties and tumor transport of drugs in clinical trials, *Journal of Controlled Release*, 326:203-221
35. Alhakamy NA, Alaofi AL, Ahmed OA, A Fahmy U, Md S, Abdulaal WH, Alfaleh MA, Chakraborty A, Berkland CJ, Dhar P (2020) Development of Lipid Membrane Based Assays to Accurately Predict the Transfection Efficiency of Cell-Penetrating Peptide-Based Gene Nanoparticles, *International Journal of Pharmaceutics*, 580:119221
36. Pressnall MM, Huayamares SG, Berkland CJ (2020) Immunostimulant Complexed With Polylysine Limits Transport and Maintains Immune Cell Activation, *Journal of Pharmaceutical Sciences*, 109(9):2836-2846
37. Griffin JD, Song JY, Sestak JO, DeKosky BJ, Berkland CJ (2020) Linking autoantigen properties to mechanisms of immunity, *Advanced Drug Delivery Reviews*, 165-166:105-116
38. Brummer G, Fang W, Smart C, Zinda B, Alissa N, Berkland C, Miller D, and Cheng N (2019) CCR2 signaling in breast carcinoma cells promotes tumor growth and invasion by promoting CCL2 and suppressing CD154 effects on the angiogenic and immune microenvironment, *Oncogene*, 39(11):2275-2289
39. Griffin JD, Song JY, Huang A, Sedlacek AR, Flannagan KL, Berkland C (2019) Antigen-specific immune decoys intercept and exhaust autoimmunity to prevent disease, *Biomaterials*, 222:119440

40. Antunez LR, Pressnall MM, Berkland C (2019) Adjuvants as Delivery Systems in Antigen-Specific Immunotherapies, *Journal of Pharmaceutical Sciences*, 108(12):3831-3841
41. Qian J and Berkland C (2019) Conformational Stability Effect of Polymeric Iron Chelators, *iScience*, 21:134-134
42. Hu Q, Myers M, Fang W, Yao M, Brummer G, Hawj J, Smart C, Berkland C, Cheng N, (2019) Role of ALDH1A1 and HTRA2 expression in CCL2/CCR2-mediated breast cancer cell growth and invasion, *Biology Open*, 8(7)
43. Lu R, Groer C, Kleindl PA, Moulder KR, Huang A, Hunt JR, Cai S, Aires DJ, Berkland C, Forrest ML, (2019) Formulation and preclinical evaluation of a toll-like receptor 7/8 agonist as an anti-tumoral immunomodulator, 306:165-176
44. Saosathan S, Khounvong J, Rungrojsakul M, Katekunlaphan T, Tima S, Chiampanichayakul S, Berkland C, Anuchapreeda S, (2019) Costunolide and parthenolide from Champi Sirindhorn (*Magnolia sirindhorniae*) inhibit leukemic cell proliferation in K562 and molt-4 cell lines, *Natural Products Research*, 28:1-5
45. Leon MA, Firdessa-Fite R, Ruffalo J, Pickens CJ, Sestak JO, Creusot R, Berkland C. (2019) Soluble Antigen Arrays as a Multivalent Display of Mimotopes recognized by Diabetogenic T cells for the Treatment of Type 1 Diabetes, *ACS Chemical Biology*, 14(7):1436-1448
46. Pickens CJ, Christopher MA, Leon MA, Pressnall MM, Johnson SN, Thati S, Sullivan BP, Berkland C. (2019) Antigen-Drug Conjugates as a Novel Therapeutic Class for the Treatment of Antigen-Specific Autoimmune Disorders, *Molecular Pharmaceutics*, 20(5):2115-2122
47. Griffin JD, Leon MA, Salash JR, Shao M, Hartwell BL, Pickens CJ, Sestak JO, Berkland C. (2019) Acute B-Cell Inhibition by Soluble Antigen Arrays is Valency-Dependent and Predicts Immunomodulation in Splenocytes, *Biomacromolecules*, 20(5):2115-2122
48. Leon MA, Wemlinger SM, Larson NR, Ruffalo JK, Middaugh CR, Cambier JC, Berkland C. (2019) Synthesis and Characterization of Multivalent Protein based Soluble Antigen Arrays for Juvenile Diabetes, *Molecular Pharmaceutics*, 16(4):1563-1572
49. Griffin JD, Christopher MA, Thati S, Salash JR, Pressnall MM, Weerasekara DB, Lunte SM, Berkland CJ. (2019) Tocopherol Emulsions as Functional Autoantigen Delivery Vehicles Evoke Therapeutic Efficacy in Experimental Autoimmune Encephalomyelitis, *Molecular Pharmaceutics*, 16(2):607-617
50. Townsend JM, Beck EC, Gehrke SH, Berkland CJ, Detamore MS (2019) Flow behavior prior to crosslinking: The need for precursor rheology for placement of hydrogels in medical applications and for 3D bioprinting, *Progress in Polymer Science*, 91:126-140
51. J.Y. Song, N.R. Larson, S. Thati, I. Torres-Vazquez, N. Martinez-Rivera, N.J. Subelzu-Aispuru, M.A. Leon, E. Rosa-Molinar, C. Schoeneich, M.L. Forrest, C.R. Middaugh, C.J. Berkland (2019) Glatiramer acetate persists at the injection site and draining lymph nodes via electrostatically-induced aggregation, *Journal of Controlled Release*, 293:36-47
52. Pacelli S, Basu S, Berkland C, Wang J, Paul A. (2018) Design of a cytocompatible hydrogel coating to modulate properties of ceramic-based scaffolds for bone repair, *Cell and Molecular Bioengineering*, 11(3):211-217

53. S Tima, S Okonogi, C Ampasavate, C Berkland, and S Anuchapreeda (2018) FLT3-specific curcumin micelles enhance activity of curcumin on FLT3-ITD overexpressing MV4-11 leukemic cells, *Drug Development and Industrial Pharmacy*, 45(3):498-505
54. M. Veisi, S.J. Johnson, K. Shafer-Pelier, J.T. Liang, C. Berkland, M. Chen, and R. Barati (2018) "Controlled release of poly(vinyl sulfonate) scale inhibitor to extend reservoir treatment lifetime" *Journal of Applied Polymer Science*, 136:47225
55. Hartwell BL, Pickens CJ, Leon M, Northrup L, Christopher M, Griffin JD, Martinez-Becerra F, Berkland C (2018) Soluble antigen arrays disarm antigen-specific B cells to promote lasting immune tolerance in experimental autoimmune encephalomyelitis, *Journal of Autoimmunity*, 93:76-88
56. Xie SX, Baoum AA, Alhakamy NA, Berkland CJ (2018) Calcium enhances gene expression when using low molecular weight poly-L-lysine delivery vehicles, *International Journal of Pharmaceutics*, 547(1-2):274-281
57. Van Kampen E, Vandervelden C, Fakhari A, Qian J, Berkland C, Gehrke SH (2018) Design of Hollow Hyaluronic Acid Cylinders for Sustained Intravitreal Protein Delivery, *Journal of Pharmaceutical Sciences*, 107(9):2354-2365
58. Ruiz S, Bowen L, Bailey MM, Berkland C (2018) Pulmonary Delivery of Ceftazidime for the Treatment of Melioidosis in a Murine Model, *Molecular Pharmaceutics*, 15(3):1371-1376
59. Townsend JM, Andrews BT, Feng Y, Wang J, Nudo RJ, Van Kampen E, Gehrke SH, Berkland CJ, Detamore MS (2018) Superior calvarial bone regeneration using pentenoate-functionalized hyaluronic acid hydrogels with devitalized tendon particles, *Acta Biomaterialia*. (2018) S1742-7061(18):30083-7
60. Townsend JM, Zabel TA, Feng Y, Wang J, Andrews BT, Nudo RJ, Berkland C, Detamore MS (2018) Effects of tissue processing on bioactivity of cartilage matrix-based hydrogels encapsulating osteoconductive particles, *Biomedical Materials*, 13(3):034108
61. Pickens CJ, Johnson SN, Pressnall MM, Leon M, Berkland C (2018) Practical Considerations, Challenges, and Limitations of Bioconjugation via Azide-Alkyne Cycloaddition, *Bioconjugate Chemistry*, 29(3):686-701
62. Dormer NH, Nelson-Brantley J, Staecker H, Berkland CJ (2018) Evaluation of a transtympanic delivery system in *Mus musculus* for extended release steroids, *European Journal of Pharmaceutical Sciences*, S0928-0987(18):30027-7
63. Northrup L, Sullivan BP, Hartwell BL, Garza A, Berkland C (2017) Co-delivery of autoantigen and dexamethasone in incomplete Freund's adjuvant ameliorates experimental autoimmune encephalomyelitis, *Journal of Controlled Release*, 266:156-165
64. Shoults CC, Kearns GL, Meyer AR, Moran J, D'Ann Pierce, Abdel-Rahman SM, Berkland CJ, and Dormer NH (2017) Pharmacokinetics of a Taste-Masked Prednisone Oral Microsphere Powder, *Journal of Bioequivalence and Bioavailability*, 9:547-554
65. J Qian, BP Sullivan, SJ Peterson, and C Berkland (2017) Nonabsorbable iron binding polymers prevent dietary iron absorption for the treatment of iron overload, *ACS Macro Letters* 6(4):350-353
66. Pacelli S, Basu S, Whitlow J, Chakravarti A, Acosta F, Varshney A, Modaresi S, Berkland C, Paul A (2017) Strategies to develop endogenous stem cell-recruiting bioactive materials for tissue repair and regeneration, *Advanced Drug Delivery Reviews*, 120:50-70
67. Gupta V, Khan Y, Berkland CJ, Laurencin CT, Detamore MS (2017) Microsphere-Based Scaffolds in Regenerative Engineering, *Annual Reviews of Biomedical Engineering*, 19:135-161

68. Kuehl C, Thati S, Sullivan B, Sestak J, Thompson M, Siahaan T, Berkland C (2017) Pulmonary Administration of Soluble Antigen Arrays Is Superior to Antigen in Treatment of Experimental Autoimmune Encephalomyelitis, *Journal of Pharmaceutical Sciences*, 106(11):3293-3302
69. Hartwell BL, Pickens CJ, Leon M, Berkland C (2017) Multivalent Soluble Antigen Arrays Exhibit High Avidity Binding and Modulation of B Cell Receptor-Mediated Signaling to Drive Efficacy against Experimental Autoimmune Encephalomyelitis, *Biomacromolecules*, 18(6):1893-1907
70. Townsend JM, Dennis SC, Whitlow J, Feng Y, Wang J, Andrews B, Nudo RJ, Detamore MS, Berkland C (2017) Colloidal Gels with Extracellular Matrix Particles and Growth Factors for Bone Regeneration in Critical Size Rat Calvarial Defects., *AAPS Journal*, 19(3):703-711
71. S Tima, S Anuchapreeda, C Ampasavate, C Berkland, S Okonogi, and (2017) Stable curcumin-loaded polymeric micellar formulation for enhancing cellular uptake and cytotoxicity to FLT3 overexpressing EoL-1 leukemic cells., *European Journal of Pharmaceutics and Biopharmaceutics*, 1114:57-68
72. Dennis SC, Whitlow J, Detamore MS, Kieweg SL, Berkland C (2017) Hyaluronic-Acid-Hydroxyapatite Colloidal Gels Combined with Micronized Native ECM as Potential Bone Defect Fillers, *Langmuir*, 33(1):206-218
73. Ishiguro S, Alhakamy N, Uppalapati D, Delzeit J, Berkland C, Tamura M (2017) Combined local pulmonary and systemic delivery of AT2R gene by modified TAT peptide nanoparticles attenuates both murine and human lung carcinoma xenografts in mice, *Journal of Pharmaceutical Sciences*, 106(1):385-394
74. Northrup L, Sullivan BP, Hartwell BL, Garza A, Berkland C (2017) Screening Immunomodulators To Skew the Antigen-Specific Autoimmune Response, *Molecular Pharmaceutics*, 14(1):66-80
75. Teresk MG, Berkland CJ, Dormer NH (2017) Deficiencies in Traditional Oral Dosage Forms and the Emergence of Controlled-Release Powder Manufacturing, *KONA: Powder and Particle Journal*, 34:91-105
76. Mohammadi Z, Sun S, Berkland C, Liang JT (2016) Chelator-mimetic multi-functionalized hydrogel: Highly efficient and reusable sorbent for Cd, Pb, and As removal from waste water, *Chemical Engineering Journal* 307:496-502
77. S Tima, S Okonogi, C Ampasavate, C Pickens, C Berkland, and S Anuchapreeda (2016) Development and Characterization of FLT3-Specific Curcumin-Loaded Polymeric Micelles as a Drug Delivery System for Treating FLT3-Overexpressing Leukemic Cells, *Journal of Pharmaceutical Sciences*, 105(12):3645-3657
78. Berkland C, Middaugh CR (2016) Overcoming formulation challenges for the next generation of vaccines, *Expert Opinion on Drug Delivery*, 13(11):1501-1502
79. Ruiz S, Bowen L, Berkland C, Bailey MM (2016) Formulation and Characterization of Nanocluster Ceftazidime for the Treatment of Acute Pulmonary Melioidosis, *Journal of Pharmaceutical Sciences*, 105(11):3399-3408
80. Gupta V, Tenny KM, Barragan M, Berkland CJ, Detamore MS (2016) Microsphere-based scaffolds encapsulating chondroitin sulfate or decellularized cartilage, *Journal of Biomaterial Applications*, 31(3):328-343

81. Fang WB, Yao M, Brummer G, Acevedo D, Alhakamy N, Berkland C, Cheng N (2016) Targeted gene silencing of CCL2 inhibits triple negative breast cancer progression by blocking cancer stem cell renewal and M2 macrophage recruitment, *Oncotarget*, 7(31):49349-49367
82. Gupta V, Lyne DV, Barragan M, Berkland CJ, Detamore MS (2016) Microsphere-based scaffolds encapsulating tricalcium phosphate and hydroxyapatite for bone regeneration, *Journal of Materials Science: Materials in Medicine*, 27(7):121
83. Kuehl C, Zhang T, Kaminskas LM, Porter CJ, Davies NM, Forrest L, Berkland C (2016) Hyaluronic Acid Molecular Weight Determines Lung Clearance and Biodistribution after Instillation, *Molecular Pharmaceutics*, 13(6):1904-14
84. Sridharan B, Mohan N, Berkland CJ, Detamore MS (2016) Material characterization of microsphere-based scaffolds with encapsulated raw materials, *Material Science and Engineering C: Materials for Biological Applications*, 63:422-8
85. Beck EC, Barragan M, Libeer TB, Kieweg SL, Converse GL, Hopkins RA, Berkland CJ, Detamore MS (2016) Chondroinduction from Naturally Derived Cartilage Matrix: A Comparison Between Devitalized and Decellularized Cartilage Encapsulated in Hydrogel Pastes, *Tissue Engineering Part A*, 22(7-8):665-679
86. Antunez LR, Livingston A, Berkland C, Dhar P (2016) Physiochemical properties of aluminum adjuvants elicit differing reorganization of phospholipid domains in model membranes, *Molecular Pharmaceutics*, 13(5):1731-7
87. Hartwell BL, Martinez-Becerra F, Chen J, Shinogle HE, Sarnowski M, Moore DS, Berkland C. (2016) Antigen-Specific Binding of Multivalent Soluble Antigen Arrays Induces Receptor Clustering and Impedes B Cell Receptor Mediated Signaling, *Biomacromolecules*, 17(3):710-22
88. Alhakamy NA, Dhar P, Berkland CJ (2016) Charge Type, Charge Spacing, and Hydrophobicity of Arginine-Rich Cell-Penetrating Peptides Dictate Gene Transfection., *Molecular Pharmaceutics*, 13(3):1047-57
89. Alhakamy NA, Ishiguro S, Uppalapati D, Berkland CJ, Tamura M (2016) AT2R Gene Delivered by Condensed Polylysine Complexes Attenuates Lewis Lung Carcinoma after Intravenous Injection or Intratracheal Spray, *Molecular Cancer Therapeutics*, 15(1):209-18
90. Hartwell BL, Smalter Hall A, Swafford D, Sullivan BP, Garza A, Sestak JO, Northrup L, Berkland C. (2015) Molecular Dynamics of Multivalent Soluble Antigen Arrays Support Two-Signal Codelivery Mechanism in Treatment of Experimental Autoimmune Encephalomyelitis, *Molecular Pharmaceutics*, 13(2):330-343
91. Northrup L, Christopher MA, Sullivan BP, Berkland C. (2016) Combining Antigen and Immunomodulators: Emerging Trends in Antigen-Specific Immunotherapy for Autoimmunity, *Advanced Drug Delivery Reviews*, 98:86-98
92. J Qian, BP Sullivan, and C Berkland (2015) pH-responsive micelle sequestant polymers inhibit fat absorption, *Biomacromolecules*, 16(8):2340-2346
93. Gupta V, Mohan N, Berkland CJ, Detamore MS (2015) Microsphere-Based Scaffolds Carrying Opposing Gradients of Chondroitin Sulfate and Tricalcium Phosphate, *Frontiers of Bioengineering and Biotechnology*, 3:96
94. Mohan N, Gupta V, Sridharan B, Mellott AJ, Easley JT, Palmer RH, Galbraith RA, Key VH, Berkland CJ, Detamore MS, (2015) Microsphere-based gradient implants for osteochondral regeneration: a long term study in sheep, *Regenerative Medicine*, 10(6):709-728

95. Sutherland AJ, Beck EC, Dennis SC, Converse GL, Hopkins RA, Berkland CJ, Detamore MS. (2015) Decellularized cartilage may be a chondroinductive material for osteochondral tissue engineering, *PLoS One*, 10(5)
96. Sullivan BP, El-Gendy N, Kuehl C, Berkland C. (2015) Pulmonary Delivery of Vancomycin Dry Powder Aerosol to Intubated Rabbits, *Molecular Pharmaceutics*, 12(8):2665-2674
97. El-Gendy N, Qian J, Eshelman K, Rivera M, Berkland C. (2015) Antibiotic activity of iron-sequestering polymers, *Biomacromolecules*, 16(5):1480-1488
98. Alhakamy NA, Elandalousi I, Ghazvini S, Berkland CJ, Dhar P. (2015) Effect of lipid headgroup charge and pH on the stability and membrane insertion potential of calcium condensed gene complexes, *Langmuir*, 31(14):4232-4245
99. Qian J, Berkland C. (2015) pH-sensitive triblock copolymers for efficient siRNA encapsulation and delivery, *Polymer Chemistry*, 6(18):3472-3479
100. Fang WB, Yao M, Jokar I, Alhakamy N, Berkland C, Chen J, Brantley-Sieders D, Cheng N. (2015) The CCL2 chemokine is a negative regulator of autophagy and necrosis in luminal B breast cancer cells. *Breast Cancer Research Treatment*, 150(2):309-320
101. W. Pornputtapitak, N. El-Gendy, and C. Berkland (2015) NanoCluster Itraconazole Formulations Provide a Potential Engineered Drug Particle Approach to Generate Effective Dry Powder Aerosols, *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 28(5):341-52
102. Beck EC, Lohman B, Tabakh D, Kieweg SL, Gehrke SH, Berkland CJ, Detamore MS, (2015) Enabling surgical placement of hydrogels through achieving paste-like rheological behavior in hydrogel precursor solutions, *Annals of Biomedical Engineering*, 43(10):2569-76
103. Hartwell BL, Antunez L, Sullivan BP, Thati S, Sestak JO, Berkland C. (2015) Multivalent Nanomaterials: Learning from Vaccines and Progressing to Antigen-Specific Immunotherapies. *Journal of Pharmaceutical Science*, 104(2):346-361
104. Thati S, Kuehl C, Hartwell B, Sestak J, Siahaan T, Forrest L, Berkland C. (2015) Routes of Administration and Dose Optimization of Soluble Antigen Arrays in Mice with Experimental Autoimmune Encephalomyelitis. *Journal of Pharmaceutical Science*, 104(2):714-721
105. Dennis SC, Bonewald L. Berkland C, Detamore MS (2014) Endochondral Ossification for Enhancing Bone Regeneration: Converging Native ECM Biomaterials and Developmental Engineering in vivo. *Tissue Engineering Part B Reviews*, 21(3):247-266
106. Sestak JO, Fakhari A, Badawi AH, Siahaan TJ, Berkland C. (2014) Structure, size, and solubility of antigen arrays determines efficacy in experimental autoimmune encephalomyelitis. *AAPS Journal* Nov;16(6):1185-93.
107. Northrup L, Sestak JO, Sullivan BP, Thati S, Hartwell BL, Siahaan TJ, Vines CM, Berkland C. (2014) Co-delivery of autoantigen and B7 pathway modulators suppresses experimental autoimmune encephalomyelitis. *AAPS Journal* Nov;16(6):1204-13.
108. C. Kuehl, N. El-Gendy, and C. Berkland (2014) NanoClusters Surface Area Allows Nanoparticle Dissolution with Microparticle Properties. *Journal of Pharmaceutical Sciences*, 103(6):1787-1796
109. S.C. Dennis, M.S. Detamore, S.L. Kieweg and C. Berkland (2014) Mapping Glycosaminoglycan-Hydroxyapatite Colloidal Gels as Potential Tissue Defect Fillers, *Langmuir*, 30(12):3528-3537

110. A.A. Baoum, C.R. Middaugh and C. Berkland (2014) DNA complexed with TAT peptide and condensed using calcium possesses unique structural features compared to PEI polyplexes, *International Journal of Pharmaceutics*, 465(1-2):11-17
111. J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland (2014) Co-Delivery of Antigen and an Immune Cell adhesion Inhibitor is Necessary for Efficacy of Soluble Antigen Arrays in Experimental Encephalomyelitis, *Molecular Therapy - Methods & Clinical Development*, 1:14008
112. W. Pornputtapitak, N. El-Gendy, J. Mermis, A. O'Brien-Ladner and C. Berkland (2014) NanoCluster budesonide formulations enable efficient drug delivery driven by mechanical ventilation, *International Journal of Pharmaceutics*, 462(1-2):19-28
113. A. Fakhari, Q. Phan, and C. Berkland (2014) Hyaluronic acid colloidal gels as self-assembling elastic biomaterials, *Journal of Biomedical Materials Research B*, 102(3):612-618
114. C. Chittasupho, J. Sestak, L. Shannon, T.J. Siahaan, C.M. Vines and C. Berkland (2014) Hyaluronic acid graft polymers displaying peptide antigen modulate dendritic cell response in vitro, *Molecular Pharmaceutics*, 11(1):367-373
115. N.A. Alhakamy, A. Kaviratna, C.J. Berkland, and P. Dhar (2013) Dynamic measurements of membrane insertion potential of synthetic cell penetrating peptides, *Langmuir*, 29(49):15336-15349
116. Q. Wang, Z. Gu, S. Jamal, M.S. Detamore MS, and C. Berkland (2013) Hybrid Hydroxyapatite Nanoparticle Colloidal Gels are Injectable Fillers for Bone Tissue Engineering, *Tissue Engineering: Part A*, 19(23-24):2586-2593
117. N.H. Dormer, V. Gupta, A.M. Scurto, C.J. Berkland, and M.S. Detamore (2013) Effect of different sintering methods on bioactivity and release of proteins from PLGA microspheres, *Materials Science and Engineering Part C*, 33(7): 4343–4351, 2013.
118. N.A. Alhakamy, A.S. Nigatu, C. Berkland, and J.D. Ramsey (2013) Noncovalently associated cell-penetrating peptides for gene delivery applications, *Therapeutic Delivery*, 4(6):741-757
119. N.A El-Gendy, A. Kaviratna, C.J. Berkland, and P. Dhar (2013) Delivery and performance of surfactant replacement therapies to treat pulmonary disorders, *Therapeutic Delivery*, 4(8):951-980
120. J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland (2013) Single-Step Grafting of Aminoxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis, *Journal of Controlled Release*, 168(3):334-340
121. A. Fakhari, Q. Phan, and C. Berkland (2013) Hyaluronic acid nanoparticles titrate the viscoelastic properties of viscosupplements, *Langmuir*, 29(17):5123-5131
122. A. Fakhari and C. Berkland (2013) Applications and Emerging Trends of Hyaluronic Acid in Tissue Engineering, as a Dermal Filler, and in Osteoarthritis Treatment, *Acta Biomaterialia*, 9(7):7081-7092
123. N.A. Alhakamy and C. Berkland (2013) Polyarginine molecular weight determines transfection efficiency of calcium condensed complexes, *Molecular Therapeutics*, 10(5):1940-1948
124. T.C. Suekama, V. Aziz, Z. Mohammadi, C. Berkland, S.H. Gehrke (2013) Synthesis and characterization of poly (N-vinyl formamide) hydrogels – A potential alternative to polyacrylamide hydrogels, *Journal of Polymer Science Part A: Polymer Chemistry*, 51:435-445
125. S. Thaiboonrod, C. Berkland, A.H. Milani, R. Ulijn and Brian R. Saunders (2013) Poly(vinylamine) Microgels: pH-Responsive Particles with High Primary Amine Contents, *Soft Matter*, 9:3920-3930

126. R. Phongpradist, S. Chiampanichayakul, S. Tima, T.J. Siahaan, C. Berkland, S. Anuchapreeda, and C. Ampasavate (2012) Potential cIBR-Conjugated PLGA Nanoparticles for Selective Targeting to Leukemic Cells, *World Academy of Science, Engineering and Technology*, 66:202-210
127. J.H. Jeon, M. Bhamidipati, B. Sridharan, A.M. Scurto, C.J. Berkland, and M.S. Detamore (2012) Tailoring of processing parameters for sintering microsphere-based scaffolds with dense phase carbon dioxide, *Journal of Biomedical Materials Research Part B*, 101(2):330-337
128. J. Yang, S.X. Xie, Y. Huang, M. Ling, J. Liu, Y. Ran, Y. Wang, J.B. Thrasher, C. Berkland, and B. Li (2012) Prostate-targeted biodegradable nanoparticles loaded with androgen receptor silencing constructs eradicate xenograft tumors in mice, *Nanomedicine*, 7(9):1297-309
129. T.R. Bagby, S. Duan, S. Cai, S. Thati, C. Berkland, D. Aires and M.L. Forrest (2012) Lymphatic trafficking kinetics and near-infrared imaging using star polymer architectures with controlled anionic character, *European Journal of Pharmaceutical Sciences*, 47(1):287-294
130. N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Processing, *Journal of Pharmaceutical Sciences*, 101(9):3425-3433
131. N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Preformulation, *Journal of Pharmaceutical Sciences*, 101(9):3434-3444
132. N. El-Gendy, P. Selvam, P. Soni and C. Berkland (2012) Development of Budesonide NanoCluster Dry Powder Aerosols: Formulation and Stability, *Journal of Pharmaceutical Sciences*, 101(9):3445-3455
133. W. Pornputtapitak, N. El-Gendy, and C. Berkland (2012) Nanocluster budesonide formulations enhance drug delivery through endotracheal tubes, *Journal of Pharmaceutical Sciences*, 101(3):1063-1072
134. M.M. Bailey, S.R. Kline, M.D. Anderson, J.L. Staymates, C. Berkland (2012) Chemically Modifiable Fluorinated Copolymer Nanoparticles for 19F-MRI Contrast Enhancement, *Journal of Applied Polymer Science*, 126(4):1218-1227
135. A. Kawabata, A. Baoum, N. Ohta, S. Jacquez, G.M. Seo, C. Berkland, and M. Tamura (2012) Intratracheal administration of a nanoparticle-based therapy with the angiotensin II type 2 receptor gene attenuates lung cancer growth, *Cancer Research*, 72(8):2057-67
136. B. Buyuktimkin, Q. Wang, P. Kiptoo, J. Stewart, C. Berkland, and T. Siahaan (2012) Vaccine-like controlled-release delivery of an immunomodulating peptide to treat experimental autoimmune encephalomyelitis, *Molecular Pharmaceutics*, 9(4):979-985
137. Dormer NH, Berkland CJ, Detamore MS (2012) Osteogenic Differentiation of Human Bone Marrow Stromal Cells in Hydroxyapatite-Loaded Microsphere-Based Scaffolds, *Tissue Engineering: Part A*, 18(7-8):757-767
138. Baoum A, Ovachenkov D, and Berkland C (2012) Calcium Condensed Cell-Penetrating Peptide Complexes Offer Highly Efficient, Low Toxicity Gene Silencing, *International Journal of Pharmaceutics*, 427(1):134-142
139. Dormer NH, Berkland CJ, Detamore MS (2012) Osteochondral interface regeneration of the rabbit knee with macroscopic gradients of bioactive signals. *Journal of Biomedical Materials Research: Part A*, 100(1):162-170
140. S. Khonddee, C. Olsen, Y. Zeng, C.R. Middaugh, and C. Berkland (2011) Non-covalent PEGylation by polyanion complexation as a means to stabilize keratinocyte growth factor-2 (KGF-2), *Biomacromolecules*, 12(11):3880-3894

141. N. El-Gendy, W. Pornputtapitak, and C. Berkland (2011) Nanoparticle agglomerates of fluticasone propionate in combination with albuterol sulfate as dry powder aerosols, *European Journal of Pharmaceutics*, 44(4):522-33
142. C. Chittasupho, T.J. Siahaan, C.M. Vines and C. Berkland (2011) Autoimmune therapies targeting costimulation and emerging trends in strategies using multivalent therapeutics, *Therapeutic Delivery*, 2(7):873-889
143. Lazebnik M, Singh M, Friis LA, Berkland CJ, Detamore MS (2011) Biomimetic method for combining the nucleus pulposus and annulus fibrosus for intervertebral disc tissue engineering, *Journal of Tissue Engineering and Regenerative Medicine*, 5(8): e179-e187
144. Dormer NH, Berkland CJ, Detamore MS (2011) Osteochondral interface regeneration of rabbit mandibular condyle with bioactive signal gradients. *Journal of Oral Maxillofacial Surgery*, 69(6):50-7
145. N. Mohan, V. Key, K.L. Caldwell, N. Dormer, C. Berkland and M.S. Detamore (2011) Continuous Gradients of Material Composition and Growth Factors for Effective Regeneration of the Osteochondral Interface, *Tissue Engineering Part A*, 17(21-22):2856-2855
146. Q. Shang, X. Wang, M. Apley, S.B. Kukanich and C. Berkland (2011) PPF Microsphere Depot Sustains NSAID Blood Levels with Infusion-Like Kinetics without 'Burst', *Journal of Veterinary Pharmacology and Therapeutics*, 35(3):231-8
147. Mohammadi Z, Xie S, Peltier E, Veisi M, Berkland C (2011) Enhancing the selectivity of an iron binding hydrogel, *European Polymer Journal*, 47(7):1485-1488
148. Khondee S, Baoum A, Siahaan, TJ, Berkland C (2011) Calcium Condensed LABL-TAT Complexes Effectively Target Gene Delivery to ICAM-1 Expressing Cells, *Molecular Pharmaceutics*, 8(3):788-98
149. C. Chittasupho, L Shannon, J.P. Krise, TJ Siahaan, CM Vines and C. Berkland (2011) Nanoparticles targeting dendritic cell surface molecules effectively block T cell conjugation and shift response, *ACS Nano*, 5(3):1693-1702
150. Mohammadi Z, Xie S, Allison G, Gehrke S and Berkland C (2011) Siderophore-Mimetic Hydrogel for Iron Chelation Therapy, *Journal of Applied Polymer Science*, 121(3):1384-1392
151. Baoum A and Berkland C (2011) Calcium Condensation of DNA Complexed with Cell-Penetrating Peptides Offers Efficient, Noncytotoxic Gene Delivery, *Journal of Pharmaceutical Sciences*, 100(5):1637-1642
152. Wang Q, Jamal S, Detamore MS, Berkland C (2011) PLGA-chitosan/PLGA-alginate nanoparticle blends as biodegradable colloidal gels for seeding human umbilical cord mesenchymal stem cells, *Journal of Biomedical Materials Research, Part A* 96(3):520-527
153. Fakhari A, Baoum A, Siahaan TJ, Le KB, Berkland C (2011) Controlling ligand surface density optimizes nanoparticle binding to ICAM-1, *Journal of Pharmaceutical Sciences*, 100(3):1045-1056
154. Janette Williams S, Huang HH, Kover K, Moore W, Berkland C, Singh M, Smirnova IV, Macgregor R, Stehno-Bittel L (2010) Reduction of diffusion barriers in isolated rat islets improves survival, but not insulin secretion or transplantation outcome, *Organogenesis* 6(2):115-24
155. Aillon KL, El-Gendy N, Dennis C, Norenberg JP, McDonald J, Berkland C (2010) Iodinated NanoClusters as an inhaled computed tomography contrast agent for lung visualization, *Molecular Pharmaceutics*, 7(4):1274-1282

156. Q. Wang, J. Wang, Q. Lu, M.S. Detamore and C. Berkland (2010) Injectable PLGA based colloidal gels for zero-order dexamethasone release in cranial defects, *Biomaterials* 31(18):4980-4986
157. Dormer NH, Berkland CJ, Detamore MS (2010) Emerging techniques in stratified designs and continuous gradients for tissue engineering of interfaces. *Annals of Biomedical Engineering*, 38(6):2121-2141
158. N. El-Gendy, K. Aillon and C. Berkland (2010) "Dry powdered aerosols of diatrizoic acid nanoparticle agglomerates as a lung contrast agent" *International Journal of Pharmaceutics*, 391(1-2):305-312
159. Xie Y, Aillon KL, Cai S, Christian JM, Davies NM, Berkland CJ, Forrest ML (2010) Pulmonary delivery of cisplatin-hyaluronan conjugates via endotracheal instillation for the treatment of lung cancer. *International Journal of Pharmaceutics*, 392(1-2):156-163
160. Dormer NH, Singh M, Wang L, Berkland CJ, Detamore MS (2010) Osteochondral interface tissue engineering using macroscopic gradients of bioactive signals. *Annals of Biomedical Engineering*, 38(6):2167-2182
161. Phongpradist R, Chittasupho C, Okonogi S, Siahaan T, Anuchapreeda S, Ampasavate C, Berkland C (2010) LFA-1 on leukemic cells as a target for therapy or drug delivery. *Current Pharmaceutical Design*, 16(21):2321-2330
162. M. Singh, N.H Dormer, M.S. Detamore and C. Berkland (2010) Three-dimensional Macroscopic Scaffolds With a Gradient in Stiffness for Functional Regeneration of Interfacial Tissues, *Journal of Biomedical Materials Research: Part A* 94(3):870-6
163. Z. Mohammadi, X. Wang and C. Berkland (2010) "Magnetic Polyvinylamine Nanoparticles by In Situ Precipitation Reaction" *The Journal of Polymer Science Part A: Polymer Chemistry* 7(4):1274-1282
164. L. Pickel, T. Matsuzuka, C. Doi, R. Ayuzawa, D.K. Maurya, S. Xie, C. Berkland and M. Tamura (2010) Overexpression of angiotensin II type 2 receptor gene induces cell death in lung adenocarcinoma cells, *Cancer Biology & Therapy* 9(4)
165. C. Chittasupho, P. Manikwar, J.P. Krise, T. Siahaan and C. Berkland (2010) "cIBR effectively targets nanoparticles to LFA-1 on acute lymphoblastic T cells" *Molecular Pharmaceutics* 7(1):146-55
166. A. Baoum, N. Dhillon, S. Buch and C. Berkland (2010) "Cationic surface modification of PLG nanoparticles offers sustained gene delivery to pulmonary epithelial cells" *Journal of Pharmaceutical Sciences* 99(5):2413-22
167. M.M. Bailey, C.M. Mahoney, E. Dempah, J. Davis, M.L. Becker, S. Khondee, E.J. Munson, and C. Berkland (2010) "Fluorinated Copolymer Nanoparticles for Multimodal Imaging Applications," *Macromolecule Rapid Communications*, 31(1):87-92
168. S. Khondee, T. Yakovleva and C. Berkland (2010) " Low charge polyvinylamine nanogels offer sustained, low-level gene expression" *Journal of Applied Polymer Science*, 118(4):1921-1932
169. M. Singh, B. Sandhu, A. Scurto, C. Berkland and M.S. Detamore (2010) "Microsphere-Based Scaffolds for Cartilage Tissue Engineering: Using Subcritical CO₂ as a Sintering Agent" *Acta Biomaterialia*, 6:137-143
170. A. Baoum, S. Xie, and C. Berkland (2009) "'Soft' Calcium Crosslinks Enable Highly Efficient Gene Transfection Using TAT Peptide" *Pharmaceutical Research*, 26(12):2619-2629

171. M. Staymates, Fletcher R, Staymates J, Gillen G and Berkland C. (2009) Production and characterization of polymer microspheres containing trace explosives using precision particle fabrication technology, *Journal of Microencapsulation* 27(5):426-35
172. S.J. Johnson, J. Trejo, M. Veisi, G.P. Willhite, J.T. Liang, and C. Berkland (2009) "Effects of divalent cations, seawater, and formation brine on positively charged polyethylenimine/dextran sulfate/chromium(III) polyelectrolyte complexes and partially hydrolyzed polyacrylamide/chromium(III) gelation" *Journal of Applied Polymer Science*, 115(2):1008-1014
173. S.K. Nune, P. Gunda, P.K. Thallapally, Y.Y. Lin, M.L. Forrest, and C. Berkland (2009) "Nanoparticles for Biomedical Imaging" *Expert Opinion on Drug Delivery*, 6(11):1175-1194
174. S.J. Williams, Q. Wang, R.R. MacGregor, T.J. Siahaan, L. Stehno-Bittel and C. Berkland (2009) "Adhesion of Pancreatic Beta Cells to Biopolymer Films" *Biopolymers*, 91(8):676-685
175. N. El-Gendy and C. Berkland (2009) "Combination chemotherapeutic dry powder aerosols via controlled nanoparticle agglomeration" *Pharmaceutical Research*, 26(7):1752-1763
176. Z. Mohammadi, A. Cole and C. Berkland (2009) "In situ synthesis of iron oxide within polyvinylamine nanoparticle reactors" *The Journal of Physical Chemistry Part C*, 113(18):7652-7658
177. C. Chittasupho, S. Xie, A. Baoum, T. Yakovleva, T.J. Siahaan and C. Berkland (2009) "ICAM-1 Targeting of Doxorubicin-Loaded PLGA Nanoparticles to Lung Epithelial Cells" *European Journal of Pharmaceutical Sciences*, 37(2):141-150
178. K.L. Aillon, Y. Xie, N. El-Gendy, C. Berkland, and M.L. Forrest (2009) "Effects of nanomaterial physicochemical properties on in vivo toxicity" *Advanced Drug Delivery Reviews*, 61(6):457-466
179. C.J. Plumley, E. Gorman, C. Bybee E. Munson and C. Berkland (2009) "Nifedipine Nanoparticle Agglomeration as a Dry Powder Aerosol Formulation Strategy" *International Journal of Pharmaceutics*, 369(1-2):136-143
180. N. El-Gendy, E. Gorman, E. Munson and C. Berkland (2009) "Budesonide Nanoparticle Agglomerates as Dry Powder Aerosols with Rapid Dissolution" *Journal of Pharmaceutical Sciences*, 98(8):2731-2746
181. M. Bailey, E. Gorman, E. Munson and C. Berkland (2008) "Pure Insulin Nanoparticle Agglomerates for Pulmonary Delivery" *Langmuir*, 24(23):13641-13620
182. M. Bailey and C. Berkland (2008) "Nanoparticle Formulations in Pulmonary Drug Delivery" *Medicinal Research Reviews*, 29(1):196-212
183. M. Singh, C. Berkland and M.S. Detamore (2008) "Strategies and Applications for Incorporating Physical and Chemical Signal Gradients in Tissue Engineering" *Tissue Engineering Part B*, 14(4):341-366
184. M. Singh, C.P. Morris, R. Ellis, M.S. Detamore and C. Berkland (2008) "Microsphere-Based Seamless Scaffolds Containing Macroscopic Gradients of Encapsulated Factors for Tissue Engineering" *Tissue Engineering Part C*, 14(4):299-309
185. L. Shi, S. Khondee, T.H. Linz and C. Berkland (2008) "Poly(N-vinylformamide) Nanogels Capable of pH-Sensitive Protein Release" *Macromolecules*, 41(17):6546-6554
186. L.J. Peek, L. Roberts and C. Berkland (2008) "PLG Nanoparticle Agglomerates as Carriers in Dry Powder Aerosol Formulation of Proteins" *Langmuir*, 24(17):9775-9783

187. M. Cordova, M. Cheng, J., Trejo, S.J., Johnson, G.P. Willhite, J.T. Liang, and C. Berkland (2008) "Delayed HPAM Gelation via Transient Sequestration of Chromium in Polyelectrolyte Complex Nanoparticles" *Macromolecules*, 41(12):4398-4404
188. M. Huang and C. Berkland (2008) "Controlled Release of Repifermin® from Polyelectrolyte Complexes Stimulates Endothelial Cell Proliferation" *Journal of Pharmaceutical Sciences*, 98(1):268-280
189. M. Huang, Z.L. Huang, M. Bilgen and C. Berkland (2008) "MRI Contrast-Enhanced Polyelectrolyte Complexes" *Nanomedicine*, 4(1):30-40
190. L.J. Peek, C.R. Middaugh and C. Berkland (2008) "Nanotechnology in Vaccine Delivery" *Advanced Drug Delivery Reviews*, 60(8):915-28
191. N. Zhang, C. Chittasupho, C. Duangrat, T. Siahaan and C. Berkland (2008) "PLGA Nanoparticle-Peptide Conjugate Effectively Targets Intercellular Cell-Adhesion Molecule-1" *Bioconjugate Chemistry*, 19(1):145-152
192. Q. Wang, L. Wang, M. Detamore and C. Berkland (2008) "Biodegradable Colloidal Gels as Moldable Tissue Engineering Scaffolds" *Advanced Materials*, 20(2):236-239
193. L. Shi, C.J. Plumley and C. Berkland (2007) "Biodegradable Nanoparticle Flocculates for Dry Powder Aerosol Formulation" *Langmuir*, 23(22):10897-901
194. M.M. Arnold, E.M. Gorman, L.J. Scheiber, E.J. Munson and C. Berkland (2007) "NanoCipro Encapsulation in Monodisperse Large Porous PLGA Microparticles" *Journal of Controlled Release*, 120:100-109
195. M. Huang, S.N. Vitharana, L.J. Peek, T. Coop, and C. Berkland (2007) "Polyelectrolyte Complexes Stabilize and Controllably Release VEGF" *Biomacromolecules*, 8(5):1607-1614
196. L. Shi and C. Berkland (2007) "Acid-Labile Polyvinylamine Micro- and Nanogel Capsules" *Macromolecules*, 40(13):4635-4643
197. C. Berkland, E.J. Pollauf, C. Raman, R. Silverman, K. Kim, and D.W. Pack (2007) "Macromolecule release from monodisperse PLG microspheres: control of release rates and investigation of release mechanism" *Journal of Pharmaceutical Sciences*, 95(5):1176-1191
198. C. Berkland, E.J. Pollauf, N. Varde, D.W. Pack, and K. Kim (2007) "Monodisperse liquid-filled biodegradable microcapsules" *Pharmaceutical Research*, 24(5):1007-1013
199. L. Shi and C. Berkland (2006) "pH-Triggered Dispersion of Nanoparticle Clusters" *Advanced Materials*, 18(17):2315-2319
200. A.L. Dunehoo, M. Anderson, S. Majumdar, N. Kobayashi, C. Berkland and T.J. Siahaan (2006) "Cell adhesion molecules for targeted drug delivery" *Journal of Pharmaceutical Sciences*, 95(9):1856-1872
201. E.J. Pollauf, C. Berkland, K. Kim, and D.W. Pack (2005) "In vitro degradation of polyanhydride/polyester core-shell double-wall microspheres" *International Journal of Pharmaceutics*, 301(1-2):294-303
202. C. Raman, C. Berkland, K. Kim, and D.W. Pack (2005) "Modeling small-molecule release from PLG microspheres: effects of polymer degradation and non-uniform drug distribution" *Journal of Controlled Release*, 103(1):149-158

203. C. Berkland, K. Kim, and D.W. Pack (2004) "Three-month, zero-order piroxicam release from monodispersed double-walled microspheres of controlled shell thickness" *Journal of Biomedical Materials Research* 70A(4):576-584
204. C. Berkland, K. Kim, and D.W. Pack (2004) "Uniform double-walled polymer microspheres of controllable shell thickness" *Journal of Controlled Release*, 96(1):101-111
205. C. Berkland, K. Kim, and D.W. Pack (2004) "Controlling Surface Nano-Structure using Flow-Limited Field-Injection Electrostatic Spraying (FFESS) of Poly-(D,L-lactide-co-glycolide)." *Biomaterials*, 25(25):5649-58
206. C. Berkland, M.J. Kipper, B. Narasimhan, K. Kim, and D.W. Pack (2004) "Microsphere Size, Precipitation Kinetics, and Drug Distribution Control Drug Release from Biodegradable Polyanhydride Microspheres." *Journal of Controlled Release*, 94(1):129-141
207. C. Berkland, K. Kim, and D.W. Pack (2003) "PLG microsphere size controls drug release rate through several competing factors." *Pharmaceutical Research*, 20(7):1055-1062
208. C. Berkland, M. King, A. Cox, K. Kim, and D.W. Pack (2002) "Precise control of PLG microsphere size provides enhanced control of drug release rate." *Journal of Controlled Release*, 82(1):137-147
209. C. Berkland, K. Kim, and D.W. Pack (2001) "Fabrication of PLG microspheres with precisely controlled and monodisperse size distributions." *Journal of Controlled Release*, 73(1):59-74

Non-Refereed Publications

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

Book Chapters

1. N. El-Gendy, M. Bailey and C. Berkland (2014) "Particle Engineering Technologies for Pulmonary Drug Delivery" *Controlled Release Science and Technology: Pulmonary Delivery*, Ed. Hugh Smyth and Anthony Hickey, 283-312

2. N.H. Dormer, C.J. Berkland and M. Singh (2014) "Monodispersed Microencapsulation Technology" Microencapsulation in the Food Industry, Ed. N. Vasisht, A.R. Khare and R. Sobel
3. M. Bailey and C. Berkland (2010) "Modified release delivery systems" Biodrug Delivery Systems, Vol. 194, Ed. Mariko Morishita and Kinam Park, 234-247

Invited Presentations

1. C. Berkland "Delivering drugs to target compartments to treat autoimmune disease, cancer, and others", The University of Utah, Salt Lake City, UT, April 4, 2022
2. C. Berkland "Designing immunotherapies for injection site retention or drainage to lymphatics", 2021 CSPS/PSJ/CC-CRS Symposium, Ottawa, Canada, May 31, 2021
3. C. Berkland "A few early lessons in entrepreneurship", University of Houston, Houston, TX, March 3, 2021
4. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", Colorado State University, Fort Collins, CO, February 2, 2021
5. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", University of Houston, Houston, TX, January 29, 2021
6. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", Washington University, St. Louis, MO, March 17, 2020
7. C. Berkland "A Discussion of Venture Capital and the Role of Scientists and Physicians", Research and Discovery Grand Rounds, The University of Kansas Medical Center, Kansas City, MO, July 20, 2020
8. C. Berkland "A Review of Clinically Tested ASIT Delivery Systems & Implications for Future Design, Antigen-Specific Immune Tolerance Drug Development, Boston, MA, February 26, 2020
9. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", Eli Lilly, Indianapolis, IN, February 20, 2020
10. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", Purdue University, February 19, 2020
11. C. Berkland "Developing a Stakeholder / Investor Pitch", Biotech Startup School, The University of Kansas, Lawrence, KS, February 4, 2020
12. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", Bristol Myers Squibb, East Brunswick, NJ, December 9, 2019
13. J. Whitlow, J. Salash, S. Huayamares, S. Crowl, B. Stottlemire, P. Dhar, M. He, C. Berkland "Remote control, remote sensing of soft materials", Honeywell Advanced Materials Consortia, Knoxville, TN, June 20, 2019
14. J. Whitlow, J. Salash, S. Huayamares, S. Crowl, B. Stottlemire, P. Dhar, M. He, C. Berkland "Remote control, remote sensing of soft materials", The University of Kansas, Lawrence, KS, January 24, 2019
15. C. Berkland "Venture capital and financing mechanisms fostering innovative start-up companies", Self Graduate Fellowship, The University of Kansas, Lawrence, KS, January 24, 2019
16. C. Berkland "Competitive Leverage", Biotech Startup School, The University of Kansas, Lawrence, KS, January 7, 2019

17. C. Berkland "Mimicking Properties of Natural Biomaterials as a Stem Cell Niche", Midwest Conference on Cell Therapy and Regenerative Medicine, Overland Park, KS, September 14, 2018
18. C. Berkland "Manufacturing Controlled Release Powders for Patient-Friendly Dosage Forms", Industrial Partners for Research in Interfacial and Materials Engineering, Minneapolis, MN, May 30, 2018
19. C. Berkland "Translating Research through New Venture Creation", The University of Kansas, Kansas City, KS, April 19, 2018
20. C. Berkland "Aerosolized ceftazidime for the prophylaxis and treatment of melioidosis", MRIGlobal, Kansas City, MO, November 8, 2017
21. C. Berkland "Drugs should be designed with delivery in mind (and vice versa)", California Institute for Biomedical Research, La Jolla, CA, November 17, 2017
22. C. Berkland "Non-viral gene delivery to mucosal surfaces", American Association of Pharmaceutical Scientists Annual Meeting, San Diego, CA, November 15, 2017
23. C. Berkland "A few early lessons in entrepreneurship", School of Biomedical Engineering, The University of Oklahoma, Norman, OK, September 1, 2017
24. C. Berkland "A few early lessons in entrepreneurship", Inaugural Distinguished Professor Lecture, The University of Kansas, Lawrence, KS, April 6, 2017
25. C. Berkland "Soluble antigen arrays as antigen-specific autoimmune therapy" Globalization of Pharmaceuticals Education Network, Lawrence, Kansas, November 12, 2016
26. C. Berkland "Entrepreneurship: Intellectual Property Strategy" Globalization of Pharmaceuticals Education Network, Lawrence, Kansas, November 12, 2016
27. C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department, The University of Illinois, Urbana-Champaign, IL, October 23, 2016
28. C. Berkland "A discussion of venture capital and the role of scientists", The University of Texas, Austin, TX, September 29, 2016
29. C. Berkland "Biomaterials and Controlled Release in Bone Tissue Engineering", The University of Kansas Medical Center, Kansas City, KS, June 15, 2016
30. C. Berkland "Early Lessons in Entrepreneurship: A Venture Capital Perspective", American Thoracic Society, San Francisco, CA, September 15, 2016
31. C. Berkland "Drug delivery systems for improving ocular therapeutics", Allergan, Irvine, CA, June 2, 2016
32. C. Berkland "Barriers to effective gene delivery", Cystic Fibrosis Foundation Pushing the Frontiers workshop, Chantilly, VA, June 3, 2015
33. C. Berkland "Polyelectrolyte complexes for gene delivery to lungs", Cystic Fibrosis Foundation Therapeutics Gene Repair and Delivery workshop, Cystic Fibrosis Foundation, Bethesda, MD, December 3, 2014
34. C. Berkland "A few early lessons in entrepreneurship", Bioengineering Department, The University of California, Berkeley, CA, October 15, 2014

35. C. Berkland "Controlled release delivery of proteins" Genentech, South San Francisco, California, December 21, 2014
36. C. Berkland "A few early lessons in entrepreneurship", Chemistry Department, The University of Kansas, Lawrence, KS, February 19, 2014
37. C. Berkland "Translatable Pharmaceutical Formulations of Aerosolized and Topical Antibiotics", U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, February 18, 2014
38. C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department 100 year Anniversary Symposium, Iowa State University, Ames, IA, September 27, 2013
39. J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland "Single-Step Grafting of Aminoxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis", ACS annual meeting, Indianapolis, Indiana, September 9, 2013
40. C. Berkland "Precision Particle Fabrication", ACS annual meeting, Indianapolis, Indiana, September 9, 2013
41. C. Berkland "Designing formulation and delivery with drug properties in mind", Gordon Conference: Preclinical Form and Formulation for Drug Discovery, Waterville Valley, New Hampshire, June 5, 2013
42. C. Berkland "Colloids and polymers for chemical delivery", Iowa State University, Ames, IA, April 19, 2013
43. S.C. Dennis, Q. Wang, S. Kieweg, M.S. Detamore and C.J. Berkland "Colloidal Gels as a New Class of 'Bingham Plastic' Biomaterials for Tissue Regeneration", CMBE annual meeting, Kohala Coast, Hawaii, January 6, 2013
44. C. Berkland "Colloids and polymers for drug and chemical delivery", Kansas State University, Manhattan, Kansas, November 5, 2012
45. C. Berkland "Uniform PLGA Microspheres Sustain NSAID Blood Levels With Zero-Order Kinetics", Controlled Release Society Annual Meeting, Quebec, Canada, July 16, 2012
46. C. Berkland "Personal and Professional Experiences in Controlled Release", Controlled Release Society Annual Meeting Young Investigator Award Presentation, Quebec, Canada, July 16, 2012
47. C. Berkland "Advanced Materials and Drug Delivery", Kimberly-Clark Heritage Lecture Series, Atlanta, Georgia, May 31, 2012
48. C. Berkland "Colloids and polymers for chemical delivery", Program of Excellence in Nanotechnology lecture series at MIT, Cambridge, Massachusetts, April 25, 2012
49. C. Berkland "Precision Particle Fabrication" Reckitt Benckiser, Hull, United Kingdom, April 11, 2012
50. C. Berkland "Precision Particle Fabrication" Kimberly-Clark, Atlanta, Georgia, April 4, 2012
51. C. Berkland "Precision Particle Fabrication" Dow Chemical, Midland, Michigan, December 7, 2011
52. J. Liang and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Schlumberger, Houston, Texas, November 14, 2011
53. C. Berkland "Engineering particles and colloids for pharmaceutical and biomaterial applications" Nagai Foundation Distinguished Lectureship for the Annual DDS Conference, Shizouka, Japan, September 15, 2011 (Keynote address)

54. C. Berkland "Nanoparticle Aerosol Formulations for Delivery of Current Drugs and Emerging Nucleic Acid Therapeutics" Defense Threat Reduction Agency, Washington D.C., August 1, 2011
55. C. Berkland "Regenerative Nanomaterials" Kinetic Concepts, Inc., San Antonio, Texas, July 11, 2011
56. C. Berkland "NanoCluster Technology and Microcapsule Approaches for Improved Dissolution and Solubilization" IQPC Improving Solubility Conference, Philadelphia, Pennsylvania, March 29, 2011
57. C. Berkland "Precision Particle Fabrication" Bioencapsulation Industrial Symposium, San Antonio, Texas, March 8, 2011
58. C. Berkland "Approaches for Synthesis, Formulation and Targeting of Various Contrast-Enhancing Colloids" General Electric Research Center, Albany, New York, January 6, 2011
59. C. Berkland "Targeted Nanomaterial Therapeutics" University of Pennsylvania, Philadelphia, Pennsylvania, January 7, 2011
60. C. Berkland "NanoClusters as Unique High Performance Aerosols" MAP Pharmaceuticals, South San Francisco, California, December 21, 2010
61. C. Berkland "Precision Particle Fabrication" Genentech, South San Francisco, California, December 21, 2010
62. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" University of Geneva, Geneva, Switzerland, October 22, 2010
63. C. Berkland "Engineering Particles: Microencapsulation and Advanced Nanoparticle Colloids" Janssen Pharmaceuticals, Beerse, Belgium, October 21, 2010
64. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" Eidgenössische Technische Hochschule, Zürich, Switzerland, October 19, 2010
65. C. Berkland "NanoClusters as Unique High Performance Aerosols" Nycomed, Konstanz, Germany, October 18, 2010
66. C. Berkland "Precision Particles for Controlled Release" Genentech, South San Francisco, California, September 21, 2010
67. C. Berkland "NanoCluster Formulation Technology" Novartis, South San Francisco, California, July 27, 2010
68. C. Berkland "Nanoparticle Formulation Approaches in Injectable and Pulmonary Medicines" The University of Missouri, Kansas City, Missouri, American Association of Pharmaceutical Scientists Student Chapter Distinguished Lecturer Series, May 26, 2009
69. C. Berkland "Particle Engineering in Aerosol and Injectable Formulations" The University of Wisconsin, Madison, Wisconsin, February 27, 2009
70. C. Berkland "Nanoparticles in Pulmonary Medicine" The University of Kansas Medical Center, Division of Pulmonary and Critical Care Medicine, Kansas City, Kansas, October 21, 2008
71. C. Berkland "Particle Engineering in Inhaled and Injectable Drug Formulations" Genentech, South San Francisco, California, July 30, 2008

72. J. Liang, P. Willhite and C. Berkland "Nanotechnology: From Drugs to Oil Refining" 3M Technical Forum, Minneapolis, Minnesota, June 26, 2008
73. C. Berkland "Translating Therapeutic Nanoparticles" Particles 2008, Orlando, Florida, May 11, 2008
74. C. Berkland "Pharmaceutical Applications of Nanoparticle Technology" Cima Labs, Brooklyn Park, Minnesota, August 27, 2007
75. C. Berkland "Engineering Nanoparticles for Biomedicine" National Institute of Standards and Technology, Gaithersburg, Maryland, May 4, 2007
76. M. Cordova, M. Cheng, P.G. Willhite, J. Liang, and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Conoco Phillips, Bartlesville, Oklahoma, March 13, 2007
77. C. Berkland "Nanoparticles for Targeted Angiogenesis: Potential Applications in Heart Disease and Spinal Cord Injury" Genentech, South San Francisco, California, November 14, 2006
78. C. Berkland "Engineering Pharmaceutical Nanoparticles" Globalization of Pharmaceuticals Education Network, Lawrence, Kansas, October 26, 2006
79. C. Berkland "Nanoparticle Agglomeration for Dry Powder Formulation" Schering Plough's Pharmaceutical Science Seminar Series in Product Development, Kenilworth, New Jersey, September 27, 2006
80. C. Berkland "Nanoparticle Technology in the Pharmaceutical Industry" AAPS Kansas City Discussion Group, Kansas City, Kansas, August 8, 2006
81. C. Berkland "Nanoclusters as a Unique Drug Delivery Platform" ACS Particles Meeting, Orlando, Florida, May 16, 2006
82. C. Berkland "Designing Particulate Vaccine Delivery Systems" Mannkind Corporation, Valencia, California, January 24, 2006
83. C. Berkland "Precision Particle Fabrication Technology" Southwest Research Institute, San Antonio, Texas, January 11, 2006
84. C. Berkland "Engineering Therapeutic Particles" guest lecturer in senior Biochemical Engineering course at Vanderbilt University, Nashville, Tennessee, November 7, 2005
85. C. Berkland "API Particle Engineering" 47th Annual International Industrial Pharmaceutical Research & Development Conference: Emerging Practices for Advancing Drug Development, Merrimac, Wisconsin, June 7, 2005
86. C. Berkland "Engineering micro- and nanoparticles for enhanced drug delivery performance" University of Kansas, Department of Chemistry, Lawrence, Kansas, March 7, 2005
87. C. Berkland "Improvements in Delivery Strategies Using Particulate Technologies to Treat Infectious Diseases" 3rd Annual Great Plains Infectious Disease Meeting, Lawrence, Kansas, September 18, 2004

Thesis Advisor and Postgraduate-Scholar Sponsor

Graduate students

Huan Gong, Pharmaceutical Chemistry
Grant Downes, Bioengineering

Dakota Even, MS Chemical Engineering
Aparna Chakravarti, PhD Bioengineering
Bryce Stottlemire (co-advisor with Mei He), PhD Bioengineering
Mary Duncan, MS Bioengineering
Justin Ruffalo, MS Bioengineering
Fah Cheuahongthong, PhD Chiang Mai University visiting
Kyle Apley, PhD Pharmaceutical Chemistry
Sebastian Huayamares, MS Bioengineering
Aric Huang, PhD Pharmaceutical Chemistry
Stephanie Johnson, PhD Pharmaceutical Chemistry
Melissa Pressnall, PhD Pharmaceutical Chemistry
Jimmy Song, PhD Pharmaceutical Chemistry
Martin Leon, PhD Chemistry
Jonathan Daniel Griffin, PhD Bioengineering
Matthew Christopher, PhD Pharmaceutical Chemistry
Chad Pickens, PhD Pharmaceutical Chemistry
Lorena Antunez, PhD Pharmaceutical Chemistry
Brittany Hartwell, PhD Bioengineering
Laura Northrup, PhD Pharmaceutical Chemistry
Christopher Kuehl, PhD Pharmaceutical Chemistry
Sharadvi Thati, PhD Pharmaceutical Chemistry
Connor Dennis, PhD Bioengineering
Adel Alghaith, MS Pharmaceutical Chemistry
Nabil Alhakamy, PhD Pharmaceutical Chemistry
Warangkana Pornputtapitak, PhD Pharmaceutical Chemistry
Auan Rungisee, PhD Chiang Mai University visiting
Abdul Baoum, PhD Pharmaceutical Chemistry
Qun Wang, PhD Chemical Engineering
Milind Singh (co-advisor with Michael Detamore), PhD Chemical Engineering
Mark Bailey, PhD Bioengineering
Carl Plumley, MS Chemical Engineering
Zahra Mohammadi, PhD Chemical Engineering
Chuda Chittasupho, PhD Pharmaceutical Chemistry
Supang Khondee, PhD Pharmaceutical Chemistry
Joshua Sestak, PhD Pharmaceutical Chemistry
Amir Fakhari, PhD Bioengineering
Matthew Arnold, MS Chemical Engineering

Postdoc sponsor

Bryce Stottlemire, KU, Lawrence
Kyle Apley, KU, Lawrence
Stephanie Johnson, KU, Lawrence
Jonathan Miller, KU, Lawrence
Jonathan Daniel Griffin, KU, Lawrence
Sharadvi Thati, KU, Lawrence
Madhuri Patil, KU, Lawrence
Bradly Sullivan, KU, Lawrence
Sara Thomas, KU, Lawrence
Ola Alawode, KU, Lawrence
Jun Chen, KU, Lawrence
Jian Qian, KU, Lawrence
Joshua Sestak, KU, Lawrence
Xiang Wang, KU, Lawrence
Qing Shang, KU, Lawrence
Nashwa El Gendy, KU, Lawrence
Sheng-Xue Xie, KU, Lawrence

Tatyana Yakovleva, KU, Lawrence
 Huili Guan, KU, Lawrence
 Azita Aghosseini, KU, Lawrence
 Kristin Aillen, KU, Lawrence
 Julieta Trejo, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
 Stephen Johnson, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
 Ying Ying Lin, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
 Parthiban Selvam, KU, Lawrence
 Yasunori Iwao, University of Shizuoka, Japan
 Satish Nune, KU, KU, Lawrence
 Navneet Dhillon, KU Medical Center, Kansas City (co-advised with Shilpa Buch)
 Lianjun Shi, KU, Lawrence
 Min Huang, KU, Lawrence
 Laura Peek, KU, Lawrence
 Samadhi Vitharana, KU, Lawrence
 Na Zhang, Associate Professor, Shandong University, China
 Chadarat Duangrat, Assistant Professor, Chiang Mai University, Thailand

Lab technicians

Utkarsh Ramesh, KU, Lawrence
 Jean Salash, KU, Lawrence
 Jon Whitlow, KU, Lawrence

Teaching Experience

Pharmaceutical Chemistry	Fall 2006
PHCH 510 Emerging Trends in Pharmaceutical Chemistry	Fall 2008
	Fall 2010
	Fall 2012
	Fall 2016
	Fall 2018
	Fall 2020
Chemical Engineering/Pharmaceutical Chemistry	Fall 2005
CPE/PHCH 715 Drug Delivery	Fall 2007
Coordinated and taught a new graduate-level course in drug delivery principles.	Fall 2009
	Fall 2011
	Fall 2013
	Spring 2016
	Spring 2017
	Spring 2018
	Spring 2019
	Spring 2020
	Spring 2021
	Spring 2022
	Spring 2023
Pharmaceutical Chemistry	Spring 2016
PHCH 626 Biopharmaceutics and Drug Delivery	Spring 2017
	Spring 2018
	Spring 2019
	Spring 2020
	Spring 2021
	Spring 2022

Spring 2023

Chemical Engineering	Spring 2008
CPE 221 Introduction to Thermodynamics	Spring 2009
	Spring 2010
Chemical Engineering	Fall 2006
CPE 111 Introduction to Chemical Engineering	
Chemical Engineering	Fall 2006
CPE 800 Graduate Seminar	
Chemical Engineering	Spring 2005
CPE 732 Advanced Transport Phenomena II	Spring 2006
Coordinated and taught the mass transport course to graduate students.	Spring 2007

Teaching Recognition

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

C&PE 656 Introduction to Biomedical Engineering (2006)

Received second most votes for “best teacher” out of 12 guest lecturers for C&PE 656. Two of these lecturers were Kemper Award winners.

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

C&PE 656 Introduction to Biomedical Engineering (2008)

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

Professional Activities

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

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

Training grants – Advisory Board; NIH NIAID – Multidimensional Vaccinogenesis
Advisory Board; NIH NIGMS – Pharmaceutical Aspects of Biotechnology

Journal Advisory Boards – Molecular Pharmaceutics (2021-present)
Journal of Pharmaceutical Sciences (2008-present)
Journal of Pharmaceutical Innovation (2008-2014)
Therapeutic Delivery (2009-2015)

Academic Advisory Boards – Center for Cancer Engineering, The Ohio State University
Center for Convergence of Bioscience and Medicine, University of Alabama
Kansas University Innovation Center, The University of Kansas
D3ET Research Program Steering Committee, The University of Kansas
Midwest Stem Cell Therapy Center, The University of Kansas
KU Strategic Initiative Committee “Promoting Well-Being, Finding Cures”

Corporate Advising – Banner Life Sciences (2015-2017)
Dauntless Pharmaceuticals (2015-2016)

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

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

Education – Director – Pharmaceutical Chemistry Undergraduate Research Program (2006-2020)
Director – Education through Outreach with Lawrence High School (NSF sponsored). More than 25 high school students have conducted research at KU through this program. (2008-2013)
Director – Biomolecular Engineering Track, BioEngineering Program at KU (2010-2015)
Drug Delivery – New graduate course offering at KU
Chemical Engineering – Module for College Prep Engineering at Lawrence High School
Short course – "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceuticals Education Network, Lawrence, KS