KinderFarms LLC, v. Genexa Inc.,

PGR2023-00051

U.S. Patent No. 11,617,795

December 12, 2024

KINDERFARMS Ex. 1054
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

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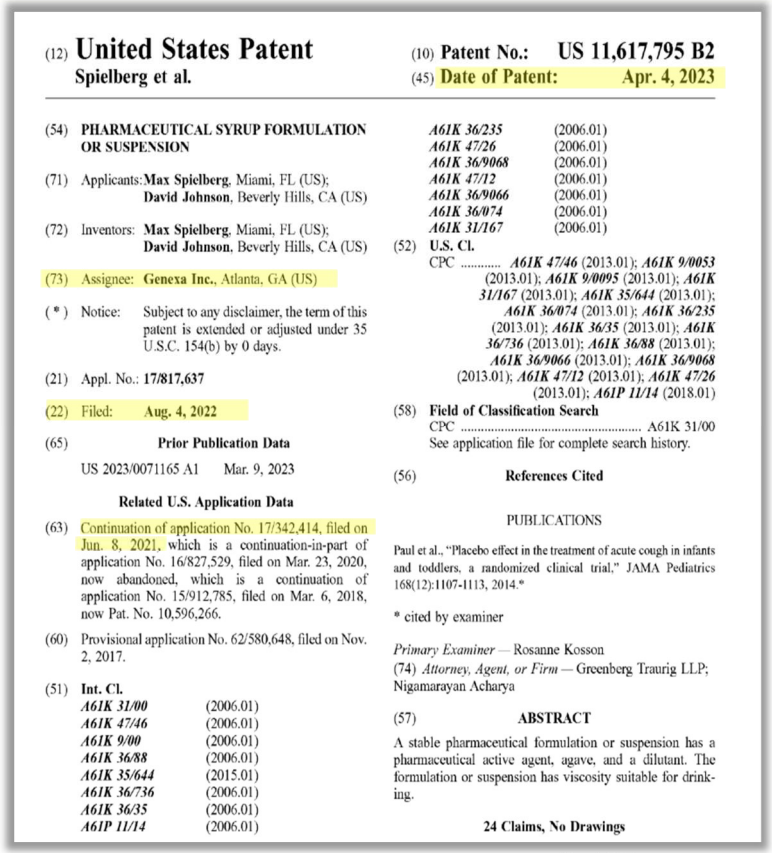
The Prosecution History of the ’795 Patent

U.S. Patent No. 11,617,795B2 (the "'795 Patent")

- **Assignee:** Genexa Inc.
- **Filing date:** Aug. 4, 2022
- **Issue date:** Apr. 4, 2023
- **Provisional filed:** Nov. 2, 2017
- **Earliest priority date:** Jun. 8, 2021 (CIP filing date)
- **24 claims** (3 independent)



(12) **United States Patent**
Spielberg et al.

(10) **Patent No.: US 11,617,795 B2**
(45) **Date of Patent: Apr. 4, 2023**

(54) **PHARMACEUTICAL SYRUP FORMULATION OR SUSPENSION**

(71) Applicants: **Max Spielberg**, Miami, FL (US); **David Johnson**, Beverly Hills, CA (US)

(72) Inventors: **Max Spielberg**, Miami, FL (US); **David Johnson**, Beverly Hills, CA (US)

(73) Assignee: **Genexa Inc.**, Atlanta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/817,637**

(22) Filed: **Aug. 4, 2022**

(65) **Prior Publication Data**

US 2023/0071165 A1 Mar. 9, 2023

Related U.S. Application Data

(63) Continuation of application No. 17/342,414, filed on Jun. 8, 2021, which is a continuation-in-part of application No. 16/827,529, filed on Mar. 23, 2020, now abandoned, which is a continuation of application No. 15/912,785, filed on Mar. 6, 2018, now Pat. No. 10,596,266.

(60) Provisional application No. 62/580,648, filed on Nov. 2, 2017.

(51) **Int. Cl.**

A61K 31/00	(2006.01)
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A61K 36/88	(2006.01)
A61K 35/644	(2015.01)
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A61K 47/26	(2006.01)
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A61K 36/9066	(2006.01)
A61K 36/074	(2006.01)
A61K 31/167	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 47/46*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/0095*** (2013.01); ***A61K 31/167*** (2013.01); ***A61K 35/644*** (2013.01); ***A61K 36/074*** (2013.01); ***A61K 36/235*** (2013.01); ***A61K 36/35*** (2013.01); ***A61K 36/736*** (2013.01); ***A61K 36/88*** (2013.01); ***A61K 36/9066*** (2013.01); ***A61K 36/9068*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/26*** (2013.01); ***A61P 11/14*** (2018.01)

(58) **Field of Classification Search**
CPC A61K 31/00
See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

Paul et al., "Placebo effect in the treatment of acute cough in infants and toddlers, a randomized clinical trial," JAMA Pediatrics 168(12):1107-1113, 2014.*

* cited by examiner

Primary Examiner — Rosanne Kosson
(74) *Attorney, Agent, or Firm* — Greenberg Traurig LLP; Nigamarayan Acharya

(57) **ABSTRACT**

A stable pharmaceutical formulation or suspension has a pharmaceutical active agent, agave, and a dilutant. The formulation or suspension has viscosity suitable for drinking.

24 Claims, No Drawings

Ex. 1001, cover page

See Pet. (Paper 2), 8-11 (citing to Ex. 1001 and Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶23, 32, 36 (citing to Ex. 1001).

The Specification of the ’795 Patent is a Wholesale Rewriting of the Original Application Filed by Genexa

Related U.S. Application Data

(63) Continuation of application No. 17/342,414, filed on Jun. 8, 2021, which is a continuation-in-part of application No. 16/827,529, filed on Mar. 23, 2020, now abandoned, which is a continuation of application No. 15/912,785, filed on Mar. 6, 2018, now Pat. No. 10,596,266.

(60) Provisional application No. 62/580,648, filed on Nov. 2, 2017.

Ex. 1001, cover page

SUMMARY OF THE INVENTION

The present invention relates to novel stabilization of liquid pharmaceutical and nutritional supplements.

In one embodiment, the present invention is a liquid composition comprising:

a primary component being an Active Pharmaceutical Ingredient (API), a nutritional supplement, or combinations thereof:

a base;

a preservative blend comprising either, Organic Cultured Dextrose, Organic Elderberry (16:1 Fruit Powder) Organic Compliant Citric Acid Organic Turmeric Root Powder Organic Fennel Seed Powder Organic Ginger Root, in a ratio of 1:0.8-1.0:0.55-0.65:0.40-0.54:0.05-0.09:0.05-0.09 or Organic Cultured Dextrose Organic Elderberry (16:1 Fruit Powder) Organic Compliant Citric Acid Organic Echinacea Purpurea Herb (6:1), in a ratio of 1:0.60-0.70:0.55-0.65:0.35-0.44.

Ex. 1009, 1-2

- The specification of the ‘529 application does not mention:
  - Any specific APIs, including acetaminophen
  - Any specific formulation viscosity, let alone a preferred viscosity range

See Pet. (Paper 2), 9-10 (citing Ex. 1001, Ex. 1009 and Ex. 1003) ; Ex. 1003 (Crowley Decl.), ¶¶36 (citing Ex. 1001), 40-41 (citing Ex. 1009).

No IDS and the Examiner Only Identified a Single Reference

Notice of References Cited	Application/Control No. 17/817,637	Applicant(s)/Patent Under Reexamination Spielberg et al.	
	Examiner ROSANNE KOSSON	Art Unit 1655	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Paul et al., "Placebo effect in the treatment of acute cough in infants and toddlers, a randomized clinical trial," JAMA Pediatrics 168(12):1107-1113, 2014.
	V	
	W	

Ex. 1002, 20

Original Investigation

Placebo Effect in the Treatment of Acute Cough in Infants and Toddlers

A Randomized Clinical Trial

Ian M. Paul, MD, MSc; Jessica S. Beiler, MPH; Julie R. Vallati, LPN; Laura M. Duda, MD; Tonya S. King, PhD

After written informed consent was obtained, each child was randomized in a partially double-blind scheme to one of the following 3 study groups: (1) pasteurized agave nectar (with natural grape flavoring, citric acid, sodium citrate, and potassium sorbate) from Zarbee's Inc, (2) natural grape-flavored water with caramel color (placebo), and (3) no treatment (**Figure 1**). For the 2 study groups receiving a study treatment, the dose volume distributed was stratified by age, with 3 mL for ages 2 to 5 months, 4 mL for ages 6 to 23 months, and 5 mL for ages 24 to 47 months. The randomization sequence was constructed by a statistician not affiliated with the study and was used to assign study groups stratified by age category with mixed block sizes. All study parents were instructed on routine care for children with nonspecific acute cough, including hydration measures, saline nasal spray use, and the use of acetaminophen or ibuprofen (for ages ≥6 months) as needed for comfort. Parents were asked not to give honey or any ex-

Ex. 1043, 1107-1108

See Pet. (Paper 2), 12-13 (citing Ex. 1002, Ex. 1043 and Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶ 38-39 (citing Ex. 1002 and Ex. 1043).

The Examiner Allowed the Claims of the '795 Patent Without the Benefit of the Prior Art Cited in Grounds 1 and 2

Examiner's Reasons for Allowance

The following is an examiner's statement of reasons for allowance. The claims as amended above are free of the prior art and recite claim language that conforms with U.S. patent practice and that is clear and complete. Paul et al. ("Placebo effect in the treatment of acute cough in infants and toddlers, a randomized clinical trial," JAMA Pediatrics 168(12):1107-1113, 2014) disclose a composition for treating night-time coughing in babies and toddlers comprising agave syrup, a flavoring agent (grape flavoring, which also serves as a diluent) and an acidic preservative (citric acid/sodium citrate). The reference discloses that this composition may be administered with acetaminophen (Tylenol®) if needed for comfort. See pp. 1108-1110. But, the acetaminophen is a separate composition; it is not part of the agave-syrup-containing composition.

Ex. 1002, 17

Prior Art NOT Provided to the Examiner

FR458

Example 1

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

Ex. 1004, 8

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

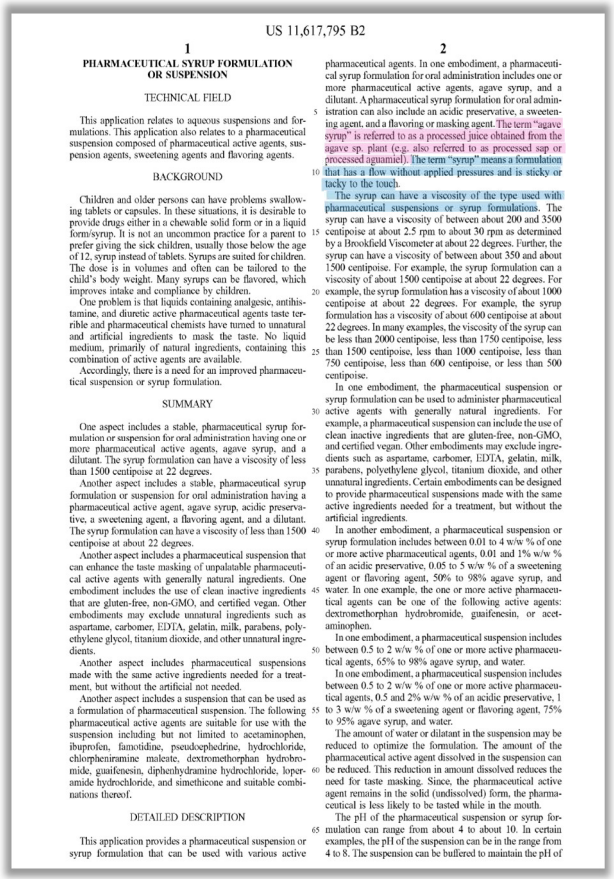
Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
Chlorpheniramine maleate	1.0 mg
Phenylephrine Hydrochloride	2.5 mg
Agave nectar	11.0 ml
Propylene Glycol	1.74 g
Ethanol (95%)	1.5 ml
Flavorants	0.05 ml
F, D & C Red #40	5.1 mg
Glycerin	750.0 mg
Aspartame	23.2 mg
Water, Purified q.s.	

Ex. 1007, 23

See Pet. (Paper 2), 5 (citing Ex. 1004 and Ex. 1007), 11-13 (citing Ex. 1002 and Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶38-39 (citing Ex. 1002).

Claim Construction

The ’795 Patent Defines “Agave Syrup” and “Syrup” Separately



US 11,617,795 B2

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PHARMACEUTICAL SYRUP FORMULATION OR SUSPENSION

TECHNICAL FIELD

This application relates to aqueous suspensions and formulations. This application also relates to a pharmaceutical suspension composed of pharmaceutical active agents, suspension agents, sweetening agents and flavoring agents.

BACKGROUND

Children and older persons can have problems swallowing tablets or capsules. In these situations, it is desirable to provide drugs either in a chewable solid form or in a liquid form/syrup. It is not an uncommon practice for a parent to prefer giving the sick children, usually those below the age of 12, syrup instead of tablets. Syrups are suited for children. The dose is in volumes and often can be tailored to the child's body weight. Many syrups can be flavored, which improves intake and compliance by children.

One problem is that liquids containing analgesic, antihistamine, and diuretic active pharmaceutical agents taste terrible and pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste. No liquid medium, primarily of natural ingredients, containing this combination of active agents are available.

Accordingly, there is a need for an improved pharmaceutical suspension or syrup formulation.

SUMMARY

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at about 22 degrees.

Another aspect includes a pharmaceutical suspension that can enhance the taste masking of unpalatable pharmaceutical active agents with generally natural ingredients. One embodiment includes the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan. Other embodiments may exclude unnatural ingredients such as aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other unnatural ingredients.

Another aspect includes pharmaceutical suspensions made with the same active ingredients needed for a treatment, but without the artificial not needed.

Another aspect includes a suspension that can be used as a formulation of pharmaceutical suspension. The following pharmaceutical active agents are suitable for use with the suspension including but not limited to acetaminophen, ibuprofen, famotidine, pseudoephedrine, hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide, guaifenesin, diphenhydramine hydrochloride, loperamide hydrochloride, and simethicone and suitable combinations thereof.

DETAILED DESCRIPTION

This application provides a pharmaceutical suspension or syrup formulation that can be used with various active

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pharmaceutical agents. In one embodiment, a pharmaceutical syrup formulation for oral administration includes one or more pharmaceutical active agents, agave syrup, and a dilutant. A pharmaceutical syrup formulation for oral administration can also include an acidic preservative, a sweetening agent, and a flavoring or masking agent. The term “agave syrup” is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel). The term “syrup” means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations. The 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. Further, the syrup can have a viscosity of between about 350 and about 1500 centipoise. For example, the syrup formulation can a viscosity of about 1500 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 1000 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 600 centipoise at about 22 degrees. In many examples, the viscosity of the syrup can be 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.

In one embodiment, the pharmaceutical suspension or syrup formulation can be used to administer pharmaceutical active agents with generally natural ingredients. For example, a pharmaceutical suspension can include the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan. Other embodiments may exclude ingredients such as aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other unnatural ingredients. Certain embodiments can be designed to provide pharmaceutical suspensions made with the same active ingredients needed for a treatment, but without the artificial ingredients.

In another embodiment, a pharmaceutical suspension or syrup formulation includes between 0.01 to 4 w/w % of one or more active pharmaceutical agents, 0.01 and 1% w/w % of an acidic preservative, 0.05 to 5 w/w % of a sweetening agent or flavoring agent, 50% to 98% agave syrup, and water. In one example, the one or more active pharmaceutical agents can be one of the following active agents: dextromethorphan hydrobromide, guaifenesin, or acetaminophen.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 65% to 98% agave syrup, and water.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 0.5 and 2% w/w % of an acidic preservative, 1 to 3 w/w % of a sweetening agent or flavoring agent, 75% to 95% agave syrup, and water.

The amount of water or dilatant in the suspension may be reduced to optimize the formulation. The amount of the pharmaceutical active agent dissolved in the suspension can be reduced. This reduction in amount dissolved reduces the need for taste masking. Since, the pharmaceutical active agent remains in the solid (undissolved) form, the pharmaceutical is less likely to be tasted while in the mouth.

The pH of the pharmaceutical suspension or syrup formulation can range from about 4 to about 10. In certain examples, the pH of the suspension can be in the range from 4 to 8. The suspension can be buffered to maintain the pH of

Ex. 1001

> The term “agave syrup” is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel).
>
> The term “syrup” means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.
>
> The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations.

Ex. 1001, 2:6-13

See Pet. (Paper 2), 7 (citing Ex. 1003), 15-16 (citing Ex. 1001), ; Ex. 1003 (Crowley Decl.), ¶¶ 28 and 93-94 (citing Ex. 1001).

The '795 Patent Does not Specify the Type or Viscosity of the Agave Syrup

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at about 22 degrees.

Ex. 1001, 1:31-41

In another embodiment, a pharmaceutical suspension or syrup formulation includes between 0.01 to 4 w/w % of one or more active pharmaceutical agents, 0.01 and 1% w/w % of an acidic preservative, 0.05 to 5 w/w % of a sweetening agent or flavoring agent, 50% to 98% agave syrup, and water. In one example, the one or more active pharmaceutical agents can be one of the following active agents: dextromethorphan hydrobromide, guaifenesin, or acetaminophen.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 65% to 98% agave syrup, and water.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 0.5 and 2% w/w % of an acidic preservative, 1 to 3 w/w % of a sweetening agent or flavoring agent, 75% to 95% agave syrup, and water.

Ex. 1001, 2:40-56

A pharmaceutical syrup formulation for oral administration can also include an acidic preservative, a sweetening agent, and a flavoring or masking agent. The term "agave syrup" is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel). The term "syrup" means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

Ex. 1001, 2:4-11

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, 5:11-19

Preparation of Suspension

100 mg of active agent can be added to 100 mL of agave (heated). The mixture is stirred, and water can is added to achieve a desired consistency. Other agents such as sweetening agent and flavoring agent can be added to the suspension.

Ex. 1001, 5:25-32

In one embodiment, the pharmaceutical suspension or syrup formulation can be prepared by mixing one or more active agents with agave and then adding water to achieve a desired consistence. One method of making a pharmaceutical syrup formulation for oral administration can include adding an amount of agave into a vessel; warming the amount of the 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

Ex. 1001, 4:42-51

Optimum masking of the taste of the pharmaceutical active agents in the pharmaceutical suspension or syrup formulation can be achieved by limiting the amount of water in the suspension. As a minimum, the amount of water present in the suspension may be limited to that amount necessary to hydrate the agave syrup. The minimum amount of water also must provide the suspension with enough aqueous base to impart the desired degree of viscosity. For example, if agave syrup is used in the suspension as a sweetener, the total amount of water contained in the suspension be in the range of about 5 to 20 grams per 100 mL of suspension. Accordingly, if a bitter or unpalatable pharmaceutical active is present in the suspension, the amount of water in all the ingredients should be kept to a minimum.

Ex. 1001, 4:11-24

See Pet. (Paper 2), 14-15; Reply (Paper 25), 20 and 22

Patent Owner Agrees That "Agave Syrup" is Not Restricted to a Particular Type of Agave Syrup

The '795 patent refers to the term "agave syrup" as "a processed juice obtained from the agave sp. Plant (e.g. also referred to as processed sap or processed aguamiel)." (Ex. 1001, 2:7-9.) The '795 patent does not limit "agave syrup" to any particular type of agave syrup. Petitioner agrees and acknowledges that a POSA would understand there are various types of agave syrup with different properties, including critically different viscosities. (*See* Pet. at 14-15 ("The '795 patent does not limit the definition to a specific type of agave syrup.").)

POR (Paper 20), 13

The Viscosity Limitations Only Pertain to the Pharmaceutical Syrup Formulations – Which Comprise More than Agave Syrup

The invention claimed is:

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.

2. The pharmaceutical syrup formulation of claim **1**, wherein the syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees.

3. The pharmaceutical syrup formulation of claim **1**, wherein the syrup formulation has a viscosity of less than 750 centipoise at about 22 degrees.

4. The pharmaceutical syrup formulation of claim **1**, wherein the syrup formulation has a viscosity of less than 600 centipoise at about 22 degrees.

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.

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.

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.

19. The formulation of claim **18**, wherein the pharmaceutical syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees.

20. The formulation of claim **18**, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.

21. The formulation of claim **18**, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.

Ex. 1001, claims 1-4, 7, 15, 18-21

See Pet. (Paper 2), 14-15; Reply (Paper 25), 10

The Problems Purportedly Addressed by the ’795 Patent

The'795 Patent Purports to Address Several Known Problems

Children and older persons can have problems swallowing tablets or capsules. In these situations, it is desirable to provide drugs either in a chewable solid form or in a liquid form/syrup. It is not an uncommon practice for a parent to prefer giving the sick children, usually those below the age of 12, syrup instead of tablets. Syrups are suited for children. The dose is in volumes and often can be tailored to the child's body weight. Many syrups can be flavored, which improves intake and compliance by children.

One problem is that liquids containing analgesic, antihistamine, and diuretic active pharmaceutical agents taste terrible and pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste. No liquid medium, primarily of natural ingredients, containing this combination of active agents are available.

Accordingly, there is a need for an improved pharmaceutical suspension or syrup formulation.

Ex. 1001, 1:12-28

See Pet. (Paper 2), 5-6; Ex. 1003 (Crowley Decl.), ¶25; Reply (Paper 25), 7

The Lack of Suitability of Solid Dosage Forms for the Very Young and the Elderly Were Known

FR458

Solid dosage forms are not suitable for children or for the elderly. This is why they are formulated in liquid dosage forms, either in a clear syrup or a suspension. Furthermore, some drugs such as cough suppressants are preferably prepared in liquid dosage forms. Some drugs are formulated in suspension either due to insufficient solubility or to mask an unpleasant taste.

Ex. 1004, 2:39-45

WO133

Acetaminophen is commonly taken as a tablet by the vast portion of the population. However, the tablet form is hard to administer in treating the elderly and the young. Therefore, liquid formulations of acetaminophen are commonly administered for these patients. However, in liquid form such as in an elixir formulation, the acetaminophen is dissolved into solution. Once dissolved, the strongly unpalatable taste of acetaminophen is found to be objectionable.

Ex. 1006. 1:13-20

See Pet. (Paper 2), 20 (citing Ex. 1004), 26 (citing Ex. 1006); Ex. 1003 (Crowley Decl.), ¶¶ 62 (citing Ex. 1004), 76 (citing Ex. 1006); Reply, 7 and 10.

The Terrible Taste of Liquid Forms of Certain Analgesics Was Known

FR458

Solid dosage forms are not suitable for children or for the elderly. This is why they are formulated in liquid dosage forms, either in a clear syrup or a suspension. Furthermore, some drugs such as cough suppressants are preferably prepared in liquid dosage forms. Some drugs are formulated in suspension either due to insufficient solubility or to mask an unpleasant taste.

Ex. 1004, 2:39-45

WO133

Acetaminophen is commonly taken as a tablet by the vast portion of the population. However, the tablet form is hard to administer in treating the elderly and the young. Therefore, liquid formulations of acetaminophen are commonly administered for these patients. However, in liquid form such as in an elixir formulation, the acetaminophen is dissolved into solution. Once dissolved, the strongly unpalatable taste of acetaminophen is found to be objectionable.

Ex. 1006. 1:13-20

See Pet. (Paper 2), 20 (citing Ex. 1004), 26 (citing Ex. 1006); Ex. 1003 (Crowley Decl.), ¶¶ 62 (citing Ex. 1004), 76 (citing Ex. 1006); Reply, 7 and 10.

The Use of Unnatural and Artificial Excipients for Taste-Masking Bitter Analgesics Was Known

FR458

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. Most of the dosage forms used do not take into account the low toxicity of the excipients and the cumulative effect of the toxins present in the excipients and the potential interactions with drugs.

Ex. 1004, 3:70-77

Heyer 2009

[0008] Due to the high amount of carbohydrate intake, one third of the US population already has obesity problems. Diabetes, arthritis, colon, heart problems and many other diseases are directly related to excessive intake of carbohydrates, most of them added to food products and medicines in the form of glucose, corn syrup, cane sugar, high fructose and starches. Artificial sweeteners were invented to lower calories with the idea of solving those problems related to high calorie intake. With time other health problems arouse, not related to obesity, but with a new series of health problems, caused by the chemical substances found in most of these artificial sweeteners.

[0009] Saccharine, phenylalanine, Aspartame, among others, have already been found to be harmful to human health in different levels. Some have been proven to be carcinogenic,

Ex. 1008, [0008]-[0009]

See Pet. (Paper 2),18 fn, 10 (citing Ex. 1008), 60 (citing Ex. 1004); Ex. 1003 (Crowley Decl.), App. D, 5, 19, 39.

The Purported Solution Was Also Known

The Solution Taught by the ’795 Patent

(57) **ABSTRACT**

A stable pharmaceutical formulation or suspension has a pharmaceutical active agent, agave, and a dilutant. The formulation or suspension has viscosity suitable for drinking.

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Ex. 1001, abstract, 1:31-35

See Pet. (Paper 2), 6-7 (citing Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶ 24 (citing Ex. 1001), 26 (citing Ex. 1001).

The Prior Art Cited in the Grounds Teaches Formulations with the Same Components

FR458

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

Ex. 1004, 8

WO742

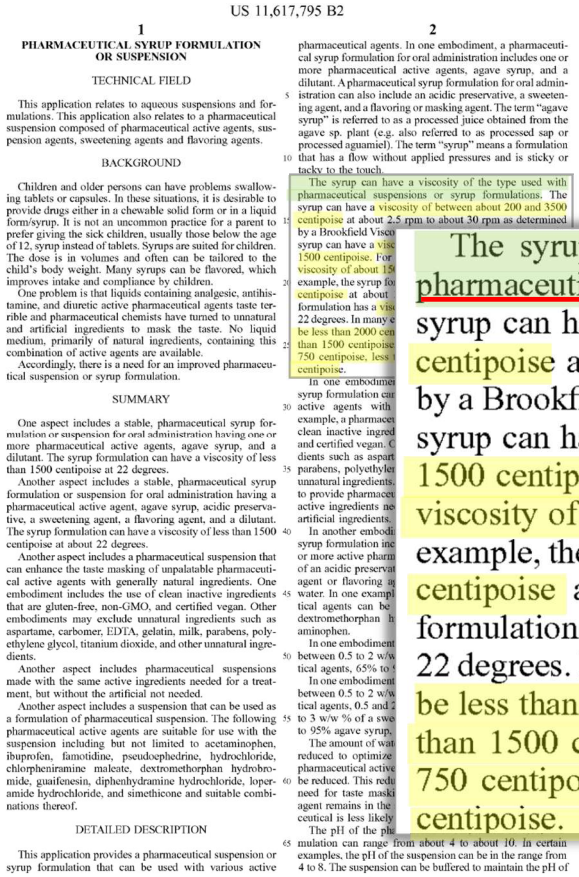
EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

See Pet. (Paper 2), 5 (citing Ex. 1004 and Ex. 1007), 20-21 (citing Ex, 1004), 29-54 (citing Ex. 1004), 56-68 (citing Ex. 1007), ; Ex. 1003 (Crowley Decl.), ¶¶ 65 (citing Ex. 1004), 69 (citing Ex. 1007).

The ’795 Patent Acknowledges its Viscosity Ranges Are Borrowed from the Art



US 11,617,795 B2

1

PHARMACEUTICAL SYRUP FORMULATION OR SUSPENSION

TECHNICAL FIELD

This application relates to aqueous suspensions and formulations. This application also relates to a pharmaceutical suspension composed of pharmaceutical active agents, suspension agents, sweetening agents and flavoring agents.

BACKGROUND

Children and older persons can have problems swallowing tablets or capsules. In these situations, it is desirable to provide drugs either in a chewable solid form or in a liquid form/syrup. It is not an uncommon practice for a parent to prefer giving the sick children, usually those below the age of 12, syrup instead of tablets. Syrups are suited for children. The dose is in volumes and often can be tailored to the child's body weight. Many syrups can be flavored, which improves intake and compliance by children.

One problem is that liquids containing analgesic, antihistamine, and diuretic active pharmaceutical agents taste terrible and pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste. No liquid medium, primarily of natural ingredients, containing this combination of active agents are available.

Accordingly, there is a need for an improved pharmaceutical suspension or syrup formulation.

SUMMARY

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a pharmaceutical suspension that can enhance the taste masking of unpalatable pharmaceutical active agents with generally natural ingredients. One embodiment includes the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan. Other embodiments may exclude unnatural ingredients such as aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other unnatural ingredients.

Another aspect includes pharmaceutical suspensions made with the same active ingredients needed for a treatment, but without the artificial not needed.

Another aspect includes a suspension that can be used as a formulation of pharmaceutical suspension. The following pharmaceutical active agents are suitable for use with the suspension including but not limited to acetaminophen, ibuprofen, famotidine, pseudoephedrine, hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide, guaifenesin, diphenhydramine hydrochloride, loperamide hydrochloride, and simethicone and suitable combinations thereof.

DETAILED DESCRIPTION

This application provides a pharmaceutical suspension or syrup formulation that can be used with various active

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pharmaceutical agents. In one embodiment, a pharmaceutical syrup formulation for oral administration includes one or more pharmaceutical active agents, agave syrup, and a dilutant. A pharmaceutical syrup formulation for oral administration can also include an acidic preservative, a sweetening agent, and a flavoring or masking agent. The term "agave syrup" is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel). The term "syrup" means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations. The 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 Visco
syrup can have a visc
1500 centipoise. For
viscosity of about 15
example, the syrup fo
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In one embodimen
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In another embodi
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tical agents can be
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In one embodiment
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tical agents, 65% to

In one embodiment
between 0.5 to 2 w/w
tical agents, 0.5 and 2
to 3 w/w % of a swe
to 95% agave syrup.

The amount of wat
reduced to optimize
pharmaceutical active
be reduced. This redu
need for taste maski
agent remains in the
ceutical is less likely

The pH of the ph
mulation can range from about 4 to about 10. In certain examples, the pH of the suspension can be in the range from 4 to 8. The suspension can be buffered to maintain the pH of

’795 Patent

The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations. The 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. Further, the syrup can have a viscosity of between about 350 and about 1500 centipoise. For example, the syrup formulation can a viscosity of about 1500 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 1000 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 600 centipoise at about 22 degrees. In many examples, the viscosity of the syrup can be 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.

Ex. 1001, col. 2, lns. 12-27

Exhibit	Oral Formulation Viscosity Range
The ’4666 Patent (Ex. 1005)	100 to 3000 cP
WO133 (Ex. 1006)	200 to 900 cP
Valinoti 2016 (Ex. 1036)	20 to 1780 cP
Neves 2010 (Ex. 1046)	2.8 to 412.3 cP
Subramaniam (Ex. 2020)	307.33-2408.33cP

Ex. 1005, 4:10-11, claim 11
Ex. 1006, 8:1-3
Ex. 1036, abstract, table 2
Ex. 1046, abstract, table 4
Ex. 2020, abstract, table 1

See Pet., (Paper 2), 7 (citing Ex. 1001, Ex. 1003, Ex. 1005 and Ex. 1006); Ex. 1003 (Crowley Decl.), ¶28 (citing Ex. 1001), ¶58 (citing Ex. 1036); Reply (Paper 25), 8, 15 (citing Ex. 1003, Ex. 1046 and Ex. 2020).

The Disclosed Viscosities Are Typical For Oral Formulations That Are Pourable and Drinkable

Dr. Crowley's Declaration

degrees." *Id.*, at 2: 12-16.[3] The '795 Patent contemplates other viscosities for the syrup, including a viscosity of less than 2,000 cP; less than 1,700 cP; less than 1,500 cP; about 1,500 cP; less than 1,000 cP; less than 750 cP; less than 600 cP; or less than 500 cP. *Id.*, at 2:17-27. The '795 Patent does not explain the importance of these viscosity ranges, but in my experience, they are all typical for orally administered liquids (i.e., solutions, syrups and elixirs) that are pourable and drinkable. Notably, the '795 Patent does not report the viscosity of the formulations described in Examples 1 and 2.

Ex. 1003, ¶28

'795 Patent

(57) **ABSTRACT**

A stable pharmaceutical formulation or suspension has a pharmaceutical active agent, agave, and a dilutant. The formulation or suspension has viscosity suitable for drinking.

Ex. 1001, cover page

See Pet., (Paper 2), 7 (citing Ex. 1001, Ex. 1003); Ex. 1003 (Crowley Decl.), ¶24 (citing Ex. 1001); Reply (Paper 25), 8-9 fn. 3 and 14-15 (citing Ex. 1003)

The Claims of the ’795 Patent

Claim 1 and Dependent Claims

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.
2.	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees
3.	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 750 centipoise at about 22 degrees
4.	The pharmaceutical syrup formulation of claim 1, wherein the syrup formulation has a viscosity of less than 600 centipoise at about 22 degrees
5	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup
6.	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup

Ex. 1001, claims 1-6

See Pet., (Paper 2), 8

Claim 7 and Dependent Claims

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.
8.	The pharmaceutical syrup formulation of claim 7, wherein the acetaminophen is between 0.01 to 2% of the formulation weight.
9.	The pharmaceutical syrup formulation of claim 7, wherein the diluent is about 5% of the formulation by weight.
10.	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is less than 98% of the formulation by weight.
11.	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is less than 95% of the formulation by weight.
12.	The pharmaceutical syrup formulation of claim 7, wherein the diluent is water.
13.	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is about 95% of the formulation by weight.
14.	The pharmaceutical syrup formulation of claim 13, wherein the acidic preservative comprises citric acid.
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.
16.	The pharmaceutical syrup formulation of claim 7, wherein the formulation is orally administered for veterinary and human use.
17.	The pharmaceutical syrup formulation of claim 7, wherein the flavoring agent is a bitter-taste-blocking ingredient.

Ex. 1001, claims 7-17 *See* Pet., (Paper 2), 8-9

Claim 18 and Dependent Claims

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.
19.	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees.
20.	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.
21.	The formulation of claim 18, wherein the pharmaceutical syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees.
22.	The formulation of claim 18, wherein the agave syrup is less than 98% of the formulation by weight.
23.	The formulation of claim 18, wherein the agave syrup is less than 95% of the formulation by weight.
24.	The formulation of claim 18, wherein the agave syrup is about 95% of the formulation by weight.

Ex. 1001, claim 18-24

See Pet., (Paper 2), 9

The State of the Art

The '795 Patent Does Not Teach Anything New

Rather, it is

"simply arrang[ing] ***old [ingredients]*** *with each performing the* ***same function*** *it had been known to perform…[a]* ***predictable use*** *of* ***prior art elements*** *according to their established functions"*

KSR Intern. Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007)

See Pet. (Paper 2), 29, 55.

Patent Owner and its Expert Agree that Agave is a Known Sweetener

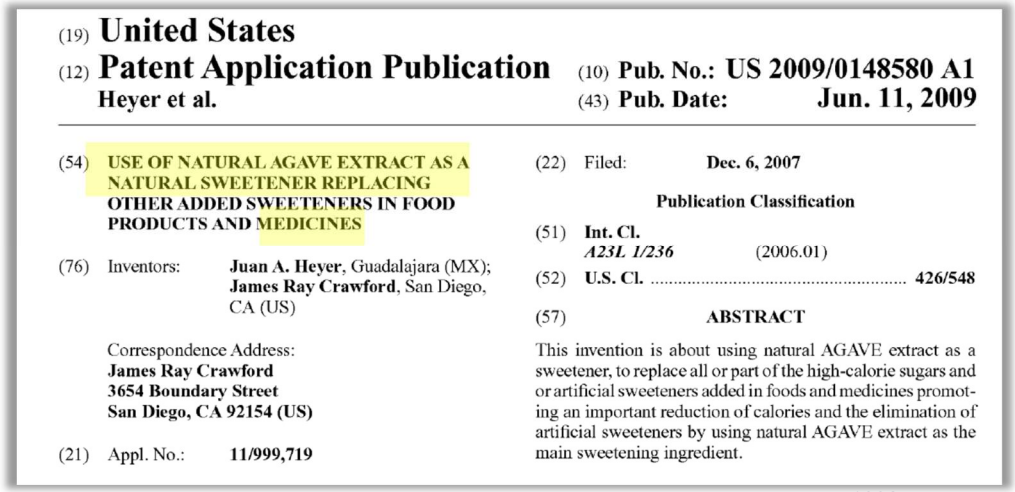
B. The Characteristics of Agave

43. Agave syrup is derived from the sap of agave plants and is a 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)).)

Ex. 2009 (Berkland Decl.), ¶43

See POR (Paper 20), 4 (citing Ex. 2009); Reply (Paper 25), 3 fn. 1 (citing Ex. 2009)

The Benefits of Using Agave Syrup in Oral Pharmaceutical Formulations Were Known to a POSITA



(19) **United States**

(12) **Patent Application Publication**

Heyer et al.

(10) **Pub. No.: US 2009/0148580 A1**

(43) **Pub. Date: Jun. 11, 2009**

(54) **USE OF NATURAL AGAVE EXTRACT AS A NATURAL SWEETENER REPLACING OTHER ADDED SWEETENERS IN FOOD PRODUCTS AND MEDICINES**

(76) Inventors: **Juan A. Heyer**, Guadalajara (MX); **James Ray Crawford**, San Diego, CA (US)

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James Ray Crawford
3654 Boundary Street
San Diego, CA 92154 (US)

(21) Appl. No.: **11/999,719**

(22) Filed: **Dec. 6, 2007**

Publication Classification

(51) **Int. Cl.**
A23L 1/236 (2006.01)

(52) **U.S. Cl.** **426/548**

(57) **ABSTRACT**

This invention is about using natural AGAVE extract as a sweetener, to replace all or part of the high-calorie sugars and or artificial sweeteners added in foods and medicines promoting an important reduction of calories and the elimination of artificial sweeteners by using natural AGAVE extract as the main sweetening ingredient.

Ex. 1008, cover page

The prior art teaches replacing refined or artificial sweeteners with natural agave syrup in oral medicines to:

- Reduce calorie intake
- Promote colon health through improved digestion and intestinal microflora growth
- Lower-glycemic index
- Provide essential vitamins and minerals (vitamins B,C,D,E, Ca, Fe, P, Mg, K, Se, Cr)
- Reduce inflammation

See Pet. (Paper 2), 3-4 (citing Ex. 1008); Ex. 1003 (Crowley Decl.), ¶¶53 and 70 (citing Ex. 1008).

Agave Syrup's Properties Are Described in the Prior Art

[0005] Commercially, other names for Agave sweetener have been "Nectar" or "Syrup" as well as other similar descriptive or extension names, however it is generally considered a SYRUP like product which can be processed as Organic, Natural or Raw. It can be light to dark in color, thicker or thinner in consistency, and even made into powder or crystals if dehydrated totally.

Ex. 1008, [0005] (cited on page 15 of the Petition)¶

It is noted that agave was cultivated for centuries by the native Indian population for fibers, food and drinks. Agave syrup or agave nectar began appearing on health food store shelves in the early 2000s. Agave syrup, also known as agave nectar, is a sweetener commonly produced in Mexico from the *Agave americana* plant (also called Century Plant). Agave syrup is similar to honey in color and texture, but it is not as viscous and flows more easily. Agave nectar is available in light or dark colors, the light liquid typically having been filtered. Agave has saponins and fructans. Inulin is a type of fructan that has many health benefits. Saponins are found in many plant roots, the most famous being ginseng.

Agave nectar is obtained from the agave plant grown in arid regions, by extracting the agave juice therefrom and processing it into a syrup. See, for example, U.S. Pat. No. 5,846,333 of Partida et al., the disclosure of which is incorporated herein by reference. Commercially, other names for Agave nectar have been "Sweetener" or "Syrup" as well as other similar descriptive or extension names. However, it is generally considered a syrup-like product which can be processed as an organic, natural, or raw state. It can be light to dark in color, thicker or thinner in consistency (viscosity), and even made into powder or crystals if dehydrated totally.

Ex. 1007, 7:5-23 (cited on page 22 of the Petition)

Table 4. Physical characterization of syrups.

Parameter	Syrup	
	Frudex 55	Agave syrup
Soluble solids (°Brix)	70.0 ± 0.1[a]	70.0 ± 0.01[a]
Density (g/ml)	1.50 ± 0.005[a]	1.49 ± 0.003[a]
Water activity (aw)	0.702 ± 0.001[a]	0.699 ± 0.002[a]
Surface tension (dinas/cm)	50.50 ± 1.83[a]	45.30 ± 0.95[b]
Viscosity (mPa-s)	224 ± 3.9[a]	212 ± 3.5[b]
Color (a*/b*)	0.04 ± 0.001[a]	0.09 ± 0.003[b]

Different letters between columns of the same line indicate statistically significant differences ($p < 0.05$).

Ex. 1030, (cited in Reply (Paper 25), 10 fn 4 for the proposition that this reference "reports agave syrup with a viscosity of 212cP")*

Like other syrups, there are several grades of agave nectar to choose from that vary in flavor, intensity, and color. As a rule of thumb, the neutral flavor of light agave nectar is best for sweetening

Ex. 1027, 22 (cited in Ex. 1003 at ¶52*)

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

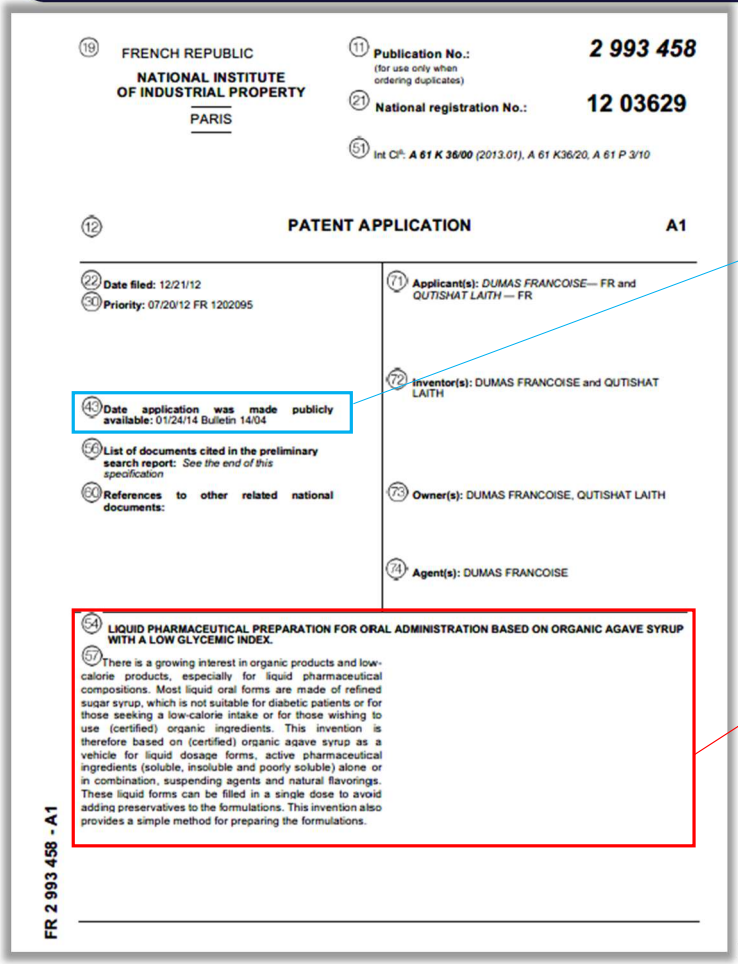
Agave syrup, a natural product with high sweetener capacity, is obtained from cooking and concentrating the juice of Agave plants. Viscosity is one of the most significant physical chemical properties in determining the quality and acceptability of syrup. Knowledge of the rheology of Agave syrup is therefore 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.

Ex. 1031, 1 (cited on p. 1 of POR and in Ex. 1003 at ¶52*)

*Ex. 1003, ¶ 52 is cited in the Petition at pp. 4fn.1 and15 and it notes that "[t]he viscosity of agave syrup is reported to be around 212mPa-S, or 212cP"

FR458 Disclosure

FR458 Overview



(19) FRENCH REPUBLIC
NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY
PARIS

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(21) National registration No.: **12 03629**

(51) Int Cl[8]: *A 61 K 36/00* (2013.01), A 61 K36/20, A 61 P 3/10

(12) **PATENT APPLICATION** **A1**

(22) **Date filed:** 12/21/12
(30) **Priority:** 07/20/12 FR 1202095

(71) **Applicant(s):** *DUMAS FRANCOISE*— FR and *QUTISHAT LAITH* — FR

(72) **Inventor(s):** DUMAS FRANCOISE and QUTISHAT LAITH

(43) **Date application was made publicly available:** 01/24/14 Bulletin 14/04

(56) **List of documents cited in the preliminary search report:** *See the end of this specification*

(60) **References to other related national documents:**

(73) **Owner(s):** DUMAS FRANCOISE, QUTISHAT LAITH

(74) **Agent(s):** DUMAS FRANCOISE

(54) **LIQUID PHARMACEUTICAL PREPARATION FOR ORAL ADMINISTRATION BASED ON ORGANIC AGAVE SYRUP WITH A LOW GLYCEMIC INDEX.**

(57) There is a growing interest in organic products and low-calorie products, especially for liquid pharmaceutical compositions. Most liquid oral forms are made of refined sugar syrup, which is not suitable for diabetic patients or for those seeking a low-calorie intake or for those wishing to use (certified) organic ingredients. This invention is therefore based on (certified) organic agave syrup as a vehicle for liquid dosage forms, active pharmaceutical ingredients (soluble, insoluble and poorly soluble) alone or in combination, suspending agents and natural flavorings. These liquid forms can be filled in a single dose to avoid adding preservatives to the formulations. This invention also provides a simple method for preparing the formulations.

FR 2 993 458 - A1

(43) **Date application was made publicly available:** 01/24/14 Bulletin 14/04

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Ex. 1004, cover page

See Pet. (Paper 2), 19-21; Ex. 1003 (Crowley Decl.), ¶¶61-65.

FR458 Discloses Oral Pharmaceutical Formulations Based on Low-Glycemic Index Organic Agave Syrup

Summary of the invention

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 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. Most of the dosage forms used do not take into account the low toxicity of the excipients and the cumulative effect of the toxins present in the excipients and the potential interactions with drugs.

Ex. 1004, 3:58-77

Claims

1- The claimed invention consists of a novel general formulation of an aqueous pharmaceutical composition for oral administration based on agave syrup.

Ex. 1004, 12

See Pet. (Paper 2), 29-30; Ex. 1003 (Crowley Decl.), ¶¶107, 114, App. D, 5, 19, 38-39.

FR458 Discloses Oral Pharmaceutical Formulations that Include Acetaminophen Suspended in Agave Syrup

The active ingredients may be chosen from, but are not limited to, the following compounds: bronchodilators, anorectics, antihistamines, dietary supplements (vitamins, minerals, fatty acids, amino acids and analogs thereof), laxatives, analgesics, antacids, H2 receptor antagonists,

Ex. 1004, 3:86-90

Examples of analgesics useful in the present invention include: morphine, codeine, meperidine, pentazocine, propoxyphene, paracetamol, allopurinol, acetylsalicylic acid, choline salicylate, ketoprofen, magnesium silicate, fenoprofen, ibuprofen, flurbiprofen, indomethacin, naproxen, and many others and their pharmaceutically-acceptable salts and mixtures thereof.

Ex. 1004, 5:127-133

Example 1

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

The xanthan gum and the agar-agar are mixed with the glycerin to obtain Solution A. The paracetamol is suspended 225 [sic] in the syrup to obtain Solution B. Solution A is added to Solution B and mixed well. The water is topped up to 100 ml and everything is mixed together. The preparation is placed in vials.

Ex. 1004, 8

Example 4

Ingredients	Quantity
Ibuprofen	2.0 g
Paracetamol	3.25 g
Certified agave syrup	35 g
Xanthan gum	0.4 g
Certified agar-agar	0.2 g
Glycerin	5 g
Sodium citrate	0.70 g
Anhydrous citric acid	0.6 g
Natural strawberry flavoring	0.01 g
Purified water	Up to 100 ml

The agar-agar and the xanthan gum are mixed with glycerin to obtain Solution A. The ibuprofen and the paracetamol are suspended in the agave syrup to make Solution B. Solution A is added to B. Then, the water is added and mixed in, and then the other ingredients are added and mixed in and then placed in vials.

Ex. 1004, 10

See Pet. (Paper 2), 19-21, 30; Ex. 1003 (Crowley Decl.), ¶122, App. D, 8-10, 25-27, 44-47.

FR458 Teaches the Use of the Same Compositions as the '795 Patent For the Same Reasons

FR458

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

Ex. 1004, 8

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. Most of the dosage forms used do not take into account the low toxicity of the excipients and the cumulative effect of the toxins present in the excipients and the potential interactions with drugs.

Ex. 1004, 3:70-77

'795 Patent

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at about 22 degrees.

Ex. 1001, 1: 31-41

rible and pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste. No liquid medium, primarily of natural ingredients, containing this combination of active agents are available.

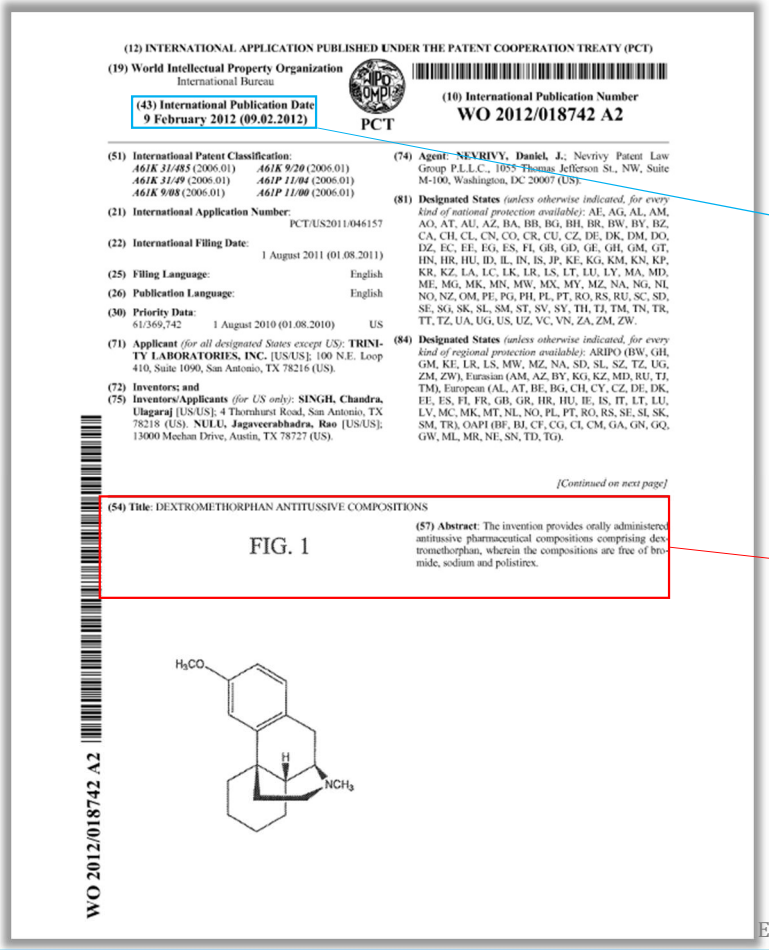
Accordingly, there is a need for an improved pharmaceutical suspension or syrup formulation.

Ex. 1001, 1: 23-28

See Pet. (Paper 2), 5-7 (citing Ex. 1001), 19-21 (citing Ex. 1004), 29-54 (citing Ex. 1001 and 1004), 60 (citing Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶24-25 (citing Ex. 1001), 63 (citing Ex. 1004).

WO742 Disclosure

WO742 Overview



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[Continued on next page]

(54) Title: DEXTROMETHORPHAN ANTITUSSIVE COMPOSITIONS

FIG. 1

(57) Abstract: The invention provides orally administered antitussive pharmaceutical compositions comprising dextromethorphan, wherein the compositions are free of bromide, sodium and polistirex.

WO 2012/018742 A2

(43) International Publication Date
9 February 2012 (09.02.2012)

(54) Title: DEXTROMETHORPHAN ANTITUSSIVE COMPOSITIONS

FIG. 1

(57) Abstract: The invention provides orally administered antitussive pharmaceutical compositions comprising dextromethorphan, wherein the compositions are free of bromide, sodium and polistirex.

Ex. 1007, cover page

See Pet. (Paper 2), 22-24; Ex. 1003 (Crowley Decl.), ¶¶66-70.

WO742 Discloses An Orally-Acceptable Pharmaceutical Carrier Based on Agave Syrup

In another aspect of the invention, there is provided a pharmaceutical composition, in dosage unit form, for oral administration comprising a safe and effective amount of dextromethorphan and an orally-acceptable pharmaceutical carrier comprising agave nectar, water and ethanol being at a pH of about 3 to about 6.5, wherein the pharmaceutical composition is free of bromide, sodium and polistirex. The composition may include from about 1 mg to about 50 mg dextromethorphan per dose. In some embodiments, the composition is an aqueous-based solution. The composition may be an agave-nectar based liquid.

Ex. 1007, 9:18-25

See Pet. (Paper 2), 22; Ex. 1003 (Crowley Decl.), ¶67.

WO742 Teaches the Same Composition as the '795 Patent

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

'795 Patent

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Ex. 1001, 1: 31-35

See Pet. (Paper 2), 5-9 (citing Ex. 1001), 22-24 and 56-68 (citing Ex. 1007); Ex. 1003 (Crowley Decl.), ¶¶ 24-26 (citing Ex. 1001), ¶¶ 66-70 and 199-265(citing Ex. 1007).

Patent Owner is Wrong About a POSITA's Knowledge of Agave Syrup

A POSITA Would Have Viewed the Use of Agave Syrup as an Ingredient in an Oral Pharmaceutical Formulations as Predictable

In these formulations, agave syrup is an

> *"**old [ingredient]...** performing the **same function** it had been known to perform"*

KSR Intern. Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007) (citing *Sakraida v. Ag pro, Inc.*, 425 U.S. 273, 282 (1976))

See Pet. (Paper 2), 29, 55; Reply (Paper 25), 3-4 fn. 1.

Patent Owner Complains That Petitioner Has Not Provided Evidence that Agave is an "Old" Oral Formulation Ingredient

> The Petition's clear and fundamental error regarding the purported viscosity of agave syrup also contradicts Petitioner's additional conclusory assertion that agave syrup is simply a well-known "old" ingredient and performs the same function it had been known to perform. If this were true, which it is not, then certainly

POR (Paper 20), 1

> Petitioner presents no evidence to support a conclusion that agave syrup, with known variable viscosity, was well-established for use in oral pharmaceutical formulations. Nor could Petitioner have done so. Genexa's agave-based products were the first. Petitioner identifies no article, textbook, treatise, approved product, regulatory guidance, pharmaceutical index, or any other evidence that agave syrup was so well-established of an ingredient for oral pharmaceutical formulations that its use would be trivial.

POR (Paper 20), 2

Patent Owner Ignores the Prior Art Cited in the Grounds that Describe Using Agave Syrup for Exactly This Purpose

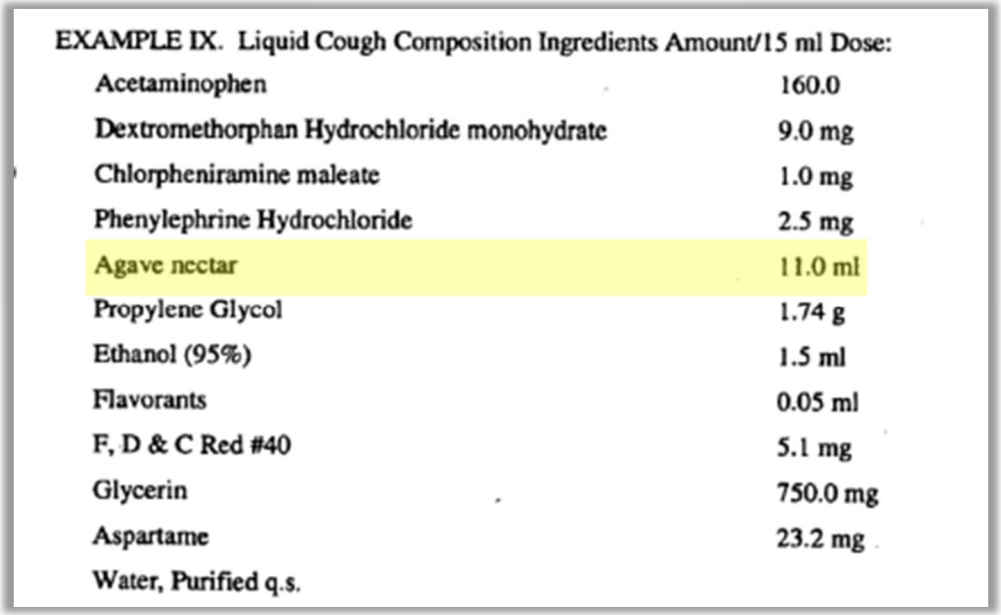
FR458

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

Ex. 1004, 8

Published January 24, 2014

WO742



EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

Published February 9, 2012

See Pet. (Paper 2), 19-22 (citing Ex. 1004), 22-24 (citing Ex. 1007); Ex. 1003 (Crowley Decl.), ¶¶61-65 (citing Ex. 1004), ¶¶66-70 (citing Ex. 1007); Reply (Paper 25), 2-3.

Patent Owner Ignores the Prior Art that Describes Using Agave Syrup for Exactly This Purpose

Heyer, 2009

USE OF NATURAL AGAVE EXTRACT AS A NATURAL SWEETENER REPLACING OTHER ADDED SWEETENERS IN FOOD PRODUCTS AND MEDICINES

Ex. 1008, cover

This invention is about using natural AGAVE extract as a sweetener, to replace all or part of the high-calorie sugars and or artificial sweeteners added in foods and medicines promoting an important reduction of calories and the elimination of artificial sweeteners by using natural AGAVE extract as the main sweetening ingredient.

Ex. 1008, abstract

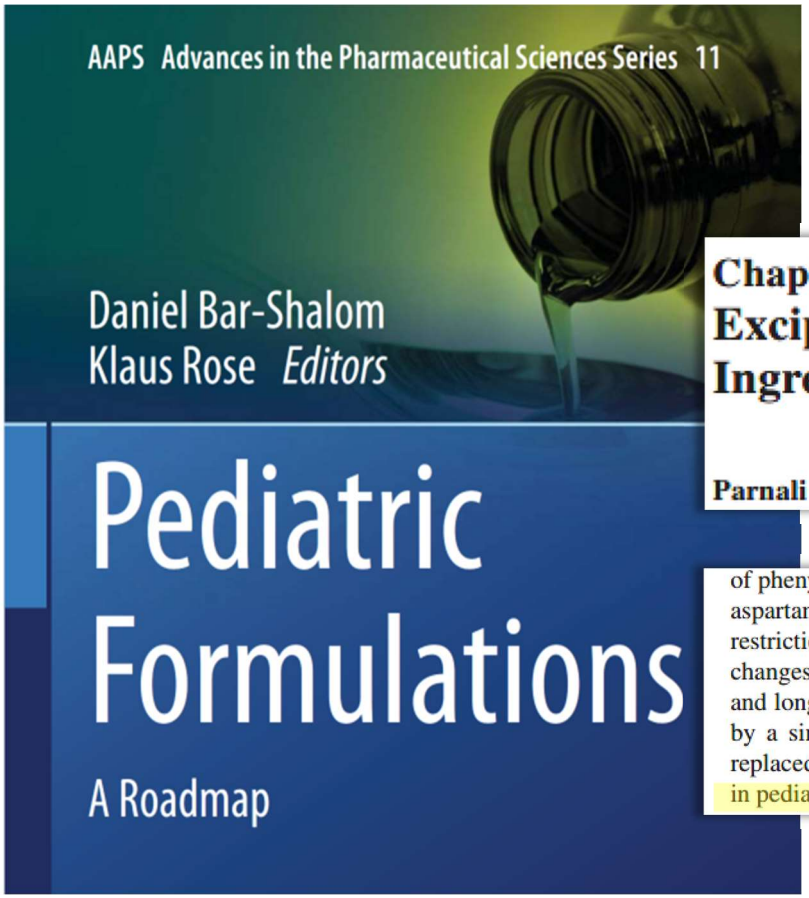
[0003] This invention is about using natural AGAVE extract as a natural sweetener to replace all or part of the high-calorie sugars and or artificial sweeteners added in foods and medicines promoting an important reduction of calories and the elimination of artificial sweeteners by using natural AGAVE as the main sweetener ingredient.

Ex. 1008, [0003]

Published June 11, 2009

See Pet. (Paper 2), 27; Ex. 1003 (Crowley Decl.), ¶70, 130 fn. 29.

Patent Owner and its Expert Ignore this Textbook Which Describes Using Agave Syrup for Exactly This Purpose



Chapter 24
Excipients and Active Pharmaceutical Ingredients

Parnali Chatterjee and Mohammed M. Alvi

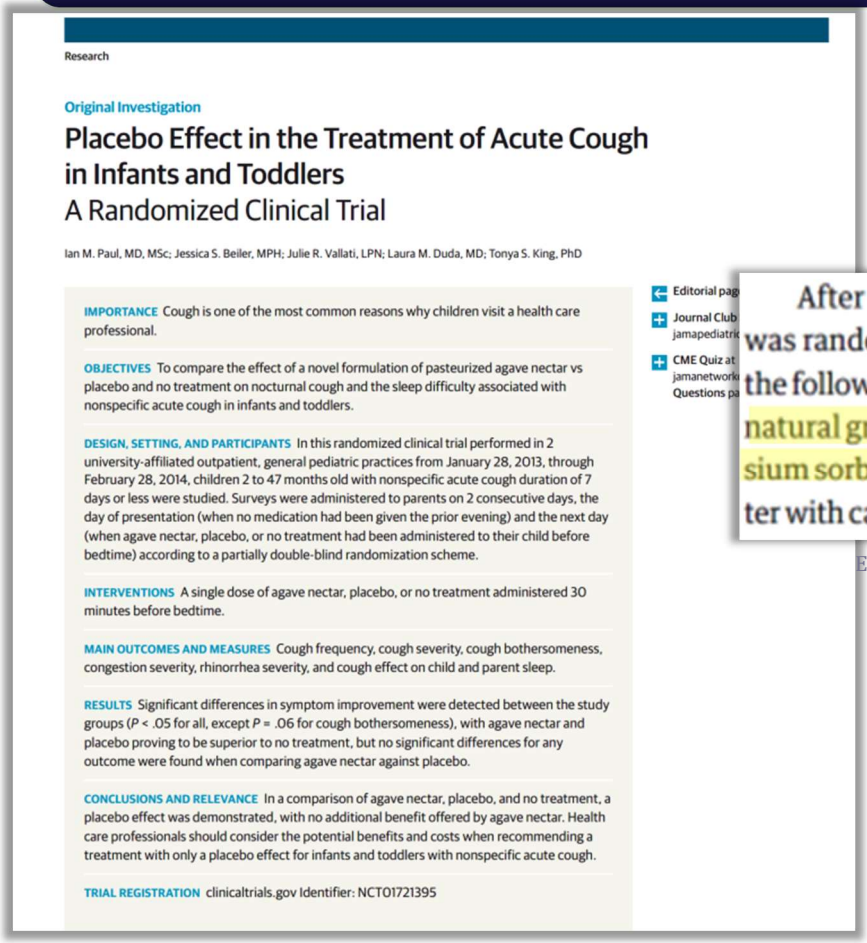
of phenylalanine could significantly rise on ingestion of aspartame. Daily intake of aspartame in children can be between 5 and 10 mg/kg, for those without any dietary restrictions. A number of adverse effects such as headaches, panic disorders, mood changes, and seizures have been reported as a result of high dose (>30 mg/kg/day) and long-term ingestion of aspartame, but none of adverse effects could be proven by a single-dose randomized double-blind clinical trial [16]. Aspartame can be replaced by stevia, date sugar, maple sugar, maple syrup molasses, and agave nectar in pediatric formulations.

Ex. 1033, 356 (cited in Petition at p. 5 and Ex. 1003 at ¶53*)

Published 2014

*Ex. 1003 (Crowley Decl.), ¶53 (cite Ex. 1033 discussing pediatric formulations) is cited on p. 5 of the Petition ("many others had proposed using agave syrup in medicines much earlier.")

Patent Owner Ignores This Peer-Reviewed Article Cited in the Petition Which Describe an Agave Syrup-Based Cough Treatment



Research

Original Investigation

Placebo Effect in the Treatment of Acute Cough in Infants and Toddlers

A Randomized Clinical Trial

Ian M. Paul, MD, MSc; Jessica S. Beiler, MPH; Julie R. Vallati, LPN; Laura M. Duda, MD; Tonya S. King, PhD

IMPORTANCE Cough is one of the most common reasons why children visit a health care professional.

OBJECTIVES To compare the effect of a novel formulation of pasteurized agave nectar vs placebo and no treatment on nocturnal cough and the sleep difficulty associated with nonspecific acute cough in infants and toddlers.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial performed in 2 university-affiliated outpatient, general pediatric practices from January 28, 2013, through February 28, 2014, children 2 to 47 months old with nonspecific acute cough duration of 7 days or less were studied. Surveys were administered to parents on 2 consecutive days, the day of presentation (when no medication had been given the prior evening) and the next day (when agave nectar, placebo, or no treatment had been administered to their child before bedtime) according to a partially double-blind randomization scheme.

INTERVENTIONS A single dose of agave nectar, placebo, or no treatment administered 30 minutes before bedtime.

MAIN OUTCOMES AND MEASURES Cough frequency, cough severity, cough bothersomeness, congestion severity, rhinorrhea severity, and cough effect on child and parent sleep.

RESULTS Significant differences in symptom improvement were detected between the study groups ($P < .05$ for all, except $P = .06$ for cough bothersomeness), with agave nectar and placebo proving to be superior to no treatment, but no significant differences for any outcome were found when comparing agave nectar against placebo.

CONCLUSIONS AND RELEVANCE In a comparison of agave nectar, placebo, and no treatment, a placebo effect was demonstrated, with no additional benefit offered by agave nectar. Health care professionals should consider the potential benefits and costs when recommending a treatment with only a placebo effect for infants and toddlers with nonspecific acute cough.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01721395

Editorial pag
Journal Club
jamapediatri
CME Quiz at
jamanetwork
Questions pa

Ex. 1043, 1107

After written informed consent was obtained, each child was randomized in a partially double-blind scheme to one of the following 3 study groups: (1) pasteurized agave nectar (with natural grape flavoring, citric acid, sodium citrate, and potassium sorbate) from Zarbee's Inc, (2) natural grape-flavored water with caramel color (placebo), and (3) no treatment (**Figure 1**).

Ex. 1043, 1108 (cited in the Petition at pp. 12-13 and in Ex. 1003 at para ¶39)

Published 2014

Patent Owner Also Ignores That Agave Syrup-Based Oral Liquid Health Products Were Available Commercially

Ex.1047. A quick review of the GRSR index confirmed that agave syrup was used in food products (Ex.1053) and in commercially available liquid health products that are orally administered to infants prior to the relevant date for obviousness, June 8, 2021. Ex.1048, Ex.1052.

Reply (Paper 25), 4 fn1

Serving suggestion:

Under 2 months	Consult your Doctor
2-5 months	3 milliliters
6-11 months	4 milliliters
1 year and older	5 milliliters

DIRECTIONS:
Suggestions for use:
- Use the dosing device enclosed with product.
- Shake well before using.
- Administer every 4-5 hours. Do not exceed 5 times per day or as directed by a physician.
- Use product within 90 days of opening.

Supplement Facts

Serving size: 3 mL Servings per container: 19

Amount per serving		%DV* Infants	%DV* Children under 4 years
Calories	20		
Total Carbohydrate	5 g	†	†
Sugars	4 g	†	†
Organic Agave Syrup	4.6 g	†	†

*Daily Value.
†Percent daily value not established.

Other ingredients: Natural Flavor, Citric Acid, Potassium Sorbate (preservative).

Available by Healthcare Professional Recommendation

52796-300-02

Natussa

HONEY FREE Baby Drops

Organic Agave

Demulcent action soothes cough, irritated throat and hoarseness*

Naturally Sweet Organic Agave

Calibrated Dropper Included

2 FL OZ (59 mL)

Dietary Supplement

No artificial colors
Gluten free

No dyes, no alcohol
No artificial flavors or sweeteners

Recommended Uses Organic Agave for:
- Occasional cough*
- Irritated throat*
- Hoarseness*

Warning: Please consult your physician immediately for worsening condition.

Keep out of reach of children.
Made in USA with foreign and domestic ingredients.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

BonGeo PHARMACEUTICALS

Manufactured for: BonGeo Pharmaceuticals, Inc.
101 Eisenhower Parkway, Ste. 300
Roseland, NJ 07068
1-844-640-7607
www.bongeopharma.net

LOT:
EXP:

Ex. 1052, 2 (cited in Reply (Paper 25) at 4 fn1)

Marketing Start Date: February 1, 2019

Patent Owner Also Ignores That Agave Syrup-Based Oral Liquid Health Products Were Available Commercially

> Ex.1047. A quick review of the GRSR index confirmed that agave syrup was used in food products (Ex.1053) and in commercially available liquid health products that are orally administered to infants prior to the relevant date for obviousness, June 8, 2021. Ex.1048, Ex.1052.

Reply (Paper 25), 4 fn1

GRIPE WATER
ginger root / fennel seed liquid

Product Information	
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GINGER (UNII: C5529G5JPQ) (GINGER - UNII:C5529G5JPQ)	GINGER	5 mg in 5 mL
FENNEL (UNII: 557II4LLC3) (FENNEL - UNII:557II4LLC3)	FENNEL	4 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
AGAVE TEQUILANA JUICE (UNII: GVG8G0207O)	
WATER (UNII: 059QF0KO0R)	
GLYCERIN (UNII: PDC6A3C0OX)	
POTASSIUM SORBATE (UNII: 1VPU26JZZ4)	

Ex. 1048, 3-5 (cited in Reply (Paper 25) at 4 fn1)

Marketing Start Date: February 15, 2017

A POSITA Would Know How to Modify an Agave Syrup to Achieve a Desired Viscosity

Petition

[1] Agave syrup can be processed as organic, natural or raw to a thicker or thinner consistency. *Id.* at [0005]. Thus, one can select the desired viscosity depending on the proposed use. Ex. 1003 at ¶52.

Pet. (Paper 2), 4 fn. 1 (cited in Reply at page 21)

Dr. Crowley's Declaration

at p. 1. A person of ordinary skill in the art would have known that the viscosity of agave syrup can be further reduced by adding additional water to the syrup. Therefore, agave syrup is relatively thinner in consistency and more pourable than other common naturally sourced sweeteners.

Ex. 1003, ¶52 (cited in Petition at 4 fn. 1 and Reply at page 20)

See Pet. (Paper 2), 4 (citing Ex. 1003).

Patent Owner Asserts that a POSITA Could Only Select an Appropriate Agave Syrup Viscosity with the '795 Patent's Teachings.

Q. And so earlier you were talking about a person of skill in the art reading the '795 patent would appreciate that they should select an agave syrup that allows them to get into the target viscosity range, correct?

A. No, what I said earlier is that a POSA would know a range of viscosities of agave is available and they would know from the patent the properties for the pharmaceutical syrup formulation and they would be able to make the decisions to create the claimed formulation.

Ex. 1051, 138:7-21

Q. And the agave that's shown in 1030, which has a viscosity of 212 centipoise would be one that would be available for a POSA to select, correct?

A. I presume so.

Q. And if that was selected, would a POSA understand that that would fall within the desired viscosity range of the final formulation?

MR. PIVOVAR: Objection to form.

A. That seems pretty loosely specified, but with the patent in hand it sounds reasonable.

Ex. 1051, 139:4-17

During his deposition, Petitioner's counsel questioned Dr. Berkland about the teachings disclosed in the '795 patent and a POSA's understanding of them. With respect to Example 1 of the '795 patent, Dr. Berkland testified as to how a POSA would have been able based on the teachings of the '795 patent, to select an appropriate agave syrup in order to achieve the claimed "pharmaceutical syrup formulation having a resulting viscosity of less than 1500," which "as a POSA, it tells me that I need to be using [an] agave syrup that can get me to that claimed result." (Ex. 2009, 116:11-23.) Yet, when asked whether "[a] POSA would have known how to do that [select an appropriate agave syrup] before the '795 patent was filed," he unequivocally testified that "***I have not seen any evidence that would lead me to believe that***." (Ex. 2009, 116:24-117:5.)

Sur-Reply (Paper 29), 18

See Reply (Paper 25), 11, 19 and 21 (citing Ex. 1051).

The ’795 Patent Says Nothing About the Viscosity of the Agave Syrup

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at about 22 degrees.

Ex. 1001, 1:31-41

In another embodiment, a pharmaceutical suspension or syrup formulation includes between 0.01 to 4 w/w % of one or more active pharmaceutical agents, 0.01 and 1% w/w % of an acidic preservative, 0.05 to 5 w/w % of a sweetening agent or flavoring agent, 50% to 98% agave syrup, and water. In one example, the one or more active pharmaceutical agents can be one of the following active agents: dextromethorphan hydrobromide, guaifenesin, or acetaminophen.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 65% to 98% agave syrup, and water.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 0.5 and 2% w/w % of an acidic preservative, 1 to 3 w/w % of a sweetening agent or flavoring agent, 75% to 95% agave syrup, and water.

Ex. 1001, 2:40-56

A pharmaceutical syrup formulation for oral administration can also include an acidic preservative, a sweetening agent, and a flavoring or masking agent. The term “agave syrup” is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel). The term “syrup” means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

Ex. 1001, 2:4-11

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, 5:11-19

Preparation of Suspension

100 mg of active agent can be added to 100 mL of agave (heated). The mixture is stirred, and water can is added to achieve a desired consistency. Other agents such as sweetening agent and flavoring agent can be added to the suspension.

Ex. 1001, 5:25-32

In one embodiment, the pharmaceutical suspension or syrup formulation can be prepared by mixing one or more active agents with agave and then adding water to achieve a desired consistence. One method of making a pharmaceutical syrup formulation for oral administration can include adding an amount of agave into a vessel; warming the amount of the 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

Ex. 1001, 4:42-51

Optimum masking of the taste of the pharmaceutical active agents in the pharmaceutical suspension or syrup formulation can be achieved by limiting the amount of water in the suspension. As a minimum, the amount of water present in the suspension may be limited to that amount necessary to hydrate the agave syrup. The minimum amount of water also must provide the suspension with enough aqueous base to impart the desired degree of viscosity. For example, if agave syrup is used in the suspension as a sweetener, the total amount of water contained in the suspension be in the range of about 5 to 20 grams per 100 mL of suspension. Accordingly, if a bitter or unpalatable pharmaceutical active is present in the suspension, the amount of water in all the ingredients should be kept to a minimum.

Ex. 1001, 4:11-24

See Reply(Paper 25), 20 and 22

The ’795 Patent Explains That the Desired Formulation Viscosity Can Be Achieved By Adding Water.

Preparation of Suspension

100 mg of active agent can be added to 100 mL of agave (heated). The mixture is stirred, and water can is added to achieve a desired consistency. Other agents such as sweetening agent and flavoring agent can be added to the suspension.

Ex. 1001, 5:25-32

necessary to hydrate the agave syrup. The minimum amount of water also must provide the suspension with enough aqueous base to impart the desired degree of viscosity. For

Ex. 1001, 4:15-17

In one embodiment, the pharmaceutical suspension or syrup formulation can be prepared by mixing one or more active agents with agave and then adding water to achieve a desired consistence. One method of making a pharmaceutical syrup formulation for oral administration can include adding an amount of agave into a vessel; warming the amount of the 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.

Ex. 1001, 4:42-52

See Pet. (Paper 2), 7-8; Reply (Paper 25), 19-20; Ex. 2009 (Berkland Decl.), ¶¶62-63

The Challenged Claims Are All Invalid

PGR2023-00051 Grounds of Institution

Grounds	Claims Challenged	35 U.S.C. §	References/Basis
1	1-24	**103**	a) FR458 and the '4666 Patent. b) FR458 and WO133. c) FR458, the '4666 Patent, and WO133.
2	1-17	**103**	a) WO742 and the '4666 Patent. b) WO742 and WO133. c) WO742, the '4666 Patent, and WO133.
3	1-24	**112(b)**	In the alternative, the following terms are indefinite because they are not defined in the specification: a) "palatable" b) "stable" c) "consisting essentially of"

See Pet. (Paper 2), 2-3

The Challenged Claims Are All Obvious

Patent Owner's Complaint that Petitioner's Grounds 1 and 2 are Ambiguous is Incorrect

> The Petition's ambiguous "and/or" combinations only further renders Petitioner's grounds more ambiguous and lacking sufficient particularity to support a finding of unpatentability of any claim because the Board should not "have to decode a petition to locate additional arguments beyond the ones clearly made."

POR (Paper 20), 37

See Reply(Paper 25), 6-7

The Petition Clearly Articulates Three Separate Prior Art Combinations For Each Obviousness Ground

When the Petition describes the prior art combinations cited in Grounds 1 and 2, it expressly describes the three separate combinations in each

Ground 1

[14] Petitioner submits that FR458 and the '4666 Patent teach each limitation and a motivation to combine with a reasonable expectation of success for these patents. Petitioner also asserts the same for FR458 and WO133. Finally, Petitioner and its declarant have provided evidence that a person of ordinary skill in the art would have a motivation to combine FR458, the '4666 Patent and WO133 with a reasonable expectation of success. Therefore, Petitioner asserts that FR458 in combination with the '4666 Patent, FR458 in combination with WO133, and FR458 in combination with the '4666 Patent and WO133 each render the claims of the '795 Patent not patentable as obvious.

Pet. (Paper 2), 28, fn14

Ground 2

[26] Petitioner submits that WO742 and the '4666 Patent teach each limitation and a motivation to combine with a reasonable expectation of success for these patents. Petitioner also asserts the same for WO742 and WO133. Finally, Petitioner and its declarant have provided evidence that a person of ordinary skill in the art would have a motivation to combine WO742, the '4666 Patent and WO133 with a reasonable expectation of success. Therefore, Petitioner asserts that WO742 in combination with the '4666 Patent, WO742 in combination with WO133, and WO742 in combination with the '4666 patent and WO133 each renders the claims of the '795 patent not patentable as obvious.

Pet. (Paper 2), 54, fn26

See Reply(Paper 25), 6-7

Afterwards, the Use of And/Or Is Confined to Headers

2. Claims 1 through 17 are Obvious over WO742 when Combined the '4666 Patent and/or WO133

(a) Claim 1

A person of ordinary skill in the art would conclude that the following combinations, WO742 in combination with the '4666 Patent, WO133 in combination with WO133, and WO742 in combination with the '4666 Patent and WO133 each disclose all the limitations of claim 1 as shown below.

Pet. (Paper 2), 29

See Reply (Paper 25), 6

Dr. Crowley Clearly Articulates the Three Separate Combinations of Prior Art Relied on in Each Obviousness Ground

129. Based upon the discussion above, which shows that FR458 combined with the '4666 Patent disclose all of the limitations of claim 1 of the '795 Patent, along with the explanation of the motivation to combine with an expectation of success, it is my opinion that these prior art references render claim 1 not patentable as obvious. Based upon the discussion above, which shows that FR458 combined with WO133 disclose all of the limitations of claim 1 of the '795 Patent, along with the explanation of the motivation to combine with an expectation of success, it is my opinion that these prior art references render claim 1 not patentable as obvious. Based upon the discussion above, which shows that FR458 combined with the '4666 Patent and WO133 disclose all of the limitations of claim 1 of the '795 Patent, along with the explanation of the motivation to combine with an expectation of success, it is my opinion that these prior art references render claim 1 not patentable as obvious.

Ex. 1003, ¶129

See Pet. (Paper 2), 33

Motivation to Combine and Reasonable Expectation of Success

Genexa Does Not Dispute

- June 8, 2021, is the earliest possible priority date to which the '795 Patent is entitled.
- FR458, the '4666 Patent, WO133 and WO742 are prior art to the '795 Patent.
- All the limitations of independent claims 1, 7 and 18 are disclosed by the prior art cited in the Petition except potentially the viscosity limitations.*
- The limitations of dependent claims 10-12, 14, 16 and 22-23 are disclosed by the prior art cited in the Petition.

* Genexa states that "none of the proposed combinations disclose viscosities that meet the claim limitations." See POR at 3. But Genexa never explains how the individual teachings of the '4666 patent and WO133 do not disclose the claimed viscosity ranges.

See POR (Paper 20), generally

KSR's Flexible Motivation to Combine Standard Still Stands

"The motivation-to-combine analysis is a flexible one.
'[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed…'"

Intel Corporation v. PACT XPP Schweiz AG, 61 F.4th 1373, 1379 (Fed. Cir. 2023)
(citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-421 (2007))

See Pet. (Paper 2), 27; Reply (25), 7-8

The Prior Art Cited in Ground 1 Are In the Same Field of Art and Address the Same Problem as The '795 Patent

Here the '795 Patent states that it was seeking to develop an oral formulation for children and the elderly that masks the taste of the APIs. Ex. 1001 at col. 1, lns. 10-28. The prior art relied upon here had the same goals.[14] FR458 is seeking to develop an oral formulation for children and the elderly that masks the unpleasant taste of the API. Ex. 1004 at 2, lns. 39-4. The '4666 Patent and WO133 identify similar rationales for developing their oral formulations that contain analgesics. Ex. 1005 at col. 1, lns. 18-29, at col. 2, lns. 3-22; Ex. 1006

Pet. (Paper 2), 28

FR458 and the ’4666 Patent Also Address Another Problem in the Art

FR458

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. Most of the dosage forms used do not take into account the low toxicity of the excipients and the cumulative effect of the toxins present in the excipients and the potential interactions with drugs.

Ex. 1004, 3: 70-77

The ‘4666 Patent

The stabilized liquid ibuprofen formulations of this invention include both sucrose sweetened and sugar free formulations suitable for administration to diabetics and other patients whose sugar intake should be restricted. Because of the bitter and unpleasant flavor of ibuprofen, it is desirable to have a product of high sweetness.

Ex. 1005, 2: 15-21

See Pet. (Paper 2), 28-29; Ex. 1003 (Crowley Decl.), ¶101; Rely (Paper 25), 3.

A POSITA Exercises Ordinary Creativity When Combining References

*"**And '[a] person of ordinary skill is also a person of ordinary creativity, not an automaton.'** So. 'in many cases[,] a person of ordinary skill will be able to **fit the teachings of multiple patents together like pieces of a puzzle.***

*That's why the motivation-to-combine analysis 'need not seek out precise teachings directed to the specific subject matter of the challenged claim, for **a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ**.'"*

Intel Corporation v. PACT XPP Schweiz AG, 61 F.4th 1373, 1379 (Fed. Cir. 2023) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-421 (2007))

See Pet. (Paper 2), 27; Reply (Paper 25), 7-8.

A POSA Would Have Been Motivated to Combine the Teachings of FR458 and WO133 and/or the '4666 Patent

FR458 teaches liquid pharmaceutical formulations for oral administration that contain, at a minimum, an API (e.g. acetaminophen), a diluent and certified organic agave syrup. WO133 teaches taste-masked acetaminophen suspensions for oral administration with viscosities that range from 200 to 900 centipoise. The '4666 Patent teaches stabilized liquid analgesic compositions with viscosities that range from 100 to 3000 centipoise. These prior art references address palatable liquid pharmaceutical compositions for oral administration that contain bitter-tasting APIs like acetaminophen and ibuprofen. As described below, a person of ordinary skill

Ex. 1003, ¶2

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. *KSR Int'l Co.*, at 417; Ex. 1003 at ¶¶101-103.

Pet. (Paper 2), 29

See Pet. (Paper 2), 19-20, 25-26; Ex. 1003 (Crowley Decl.), ¶¶62, 74, 80, 100-103; Reply (Paper 25), 2-3

The Prior Art Cited in Ground 2 Are In the Same Field of Art and Pertain to Oral Formulations with Analgesic

A person of ordinary skill in the art would look to the disclosure of a formulation that seeks to provide a safe oral formulation for patients and combine that with existing prior art references that also discuss oral formulations of APIs. Ex. 1003 at ¶ 197. These references are in the same field and each discuss the creation of oral formulations with an analgesic. Ex. 1003 at ¶ 196. The fact that each of the references discuss acetaminophen would provide an additional rationale for a person of ordinary skill in the art to combine the references. Ex. 1003 at ¶ 196. Moreover, a person of ordinary skill in the art would have been motivated to combine these references because such a person would have known that antitussives like dextromethorphan are often combined with analgesics like acetaminophen and ibuprofen in over-the-counter liquid cough and cold formulations. Ex. 1003 at ¶ 197.

Pet. (Paper 2), 55

A POSITA Would Combine WO742's Safer Antitussive Formulation with the Analgesic Formulations of the Secondary References

Like WO742, the '4666 Patent and WO133 identify pharmaceutical oral formulations that include acetaminophen as an analgesic. Ex. 1005 at col. 1, lns. 28-35; Ex. 1066 at 1, lns. 3-9. A person of ordinary skill in the art would look to the disclosure of a formulation that seeks to provide a safe oral formulation for patients and combine that with existing prior art references that also discuss oral formulations of APIs. Ex. 1003 at ¶ 197. These references are in the same field and each discuss the creation of oral formulations with an analgesic. Ex. 1003 at ¶ 196. The fact that each of the references discuss acetaminophen would provide an additional rationale for a person of ordinary skill in the art to combine the references. Ex. 1003 at ¶ 196.

Pet. (Paper 2), 55

A POSA Would Have Been Motivated to Combine the Teachings of WO742 and WO133 and/or the '4666 Patent Like Puzzle Pieces

all of the limitations of claims 1-17 of the '795 Patent. WO742 teaches orally administered antitussive compositions that contain acetaminophen and agave nectar.

agave syrup. WO133 teaches taste-masked acetaminophen suspensions for oral administration with viscosities that range from 200 to 900 centipoise. The '4666 Patent teaches stabilized liquid analgesic compositions with viscosities that range from 100 to 3000 centipoise. These prior art references address palatable liquid pharmaceutical compositions for oral administration that contain bitter-tasting APIs like acetaminophen and ibuprofen. As described below, a person of ordinary skill

Ex. 1003, ¶¶2-3

¶ 197. These references are in the same field and each discuss the creation of oral formulations with an analgesic. Ex. 1003 at ¶ 196. The fact that each of the references discuss acetaminophen would provide an additional rationale for a person of ordinary skill in the art to combine the references. Ex. 1003 at ¶ 196. Moreover,

Pet. (Paper 2), 55

at 417. Therefore, a person of ordinary skill in the art would be motivated to combine these teachings and would have a reasonable expectation of success in so doing. Ex. 1003 at ¶¶ 195-198.

Pet. (Paper 2), 55

See Pet. (Paper 2),22-23, 25-26; Ex. 1003 (Crowley Decl.), ¶¶67, 74, 80, 195-198; Reply (Paper 25), 4-5

As Noted by the Board, a POSITA's Predictable Use of Prior Art Elements is Obvious

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007)

See Institution Decision (Paper 8), 22

A POSITA Would Have Had a Reasonable Expectation of Success in Combining the Prior Art Elements from Grounds 1 and 2

102. A skilled person would have had a reasonable expectation of success in combining these three references. All of the ingredients disclosed in these references were known to the skilled person and could be combined by routine methods. Furthermore, since each ingredient in the combination would be carrying out a function it is already known to perform in an oral analgesic formulation, the result of this combination would have been predictable to one of ordinary skill in the art.

Ex. 1003, ¶102

See Pet. (Paper 2), 29, 55; Reply (Paper 25), 3-4; Ex. 1003 (Crowley Decl.), ¶¶ 102, 197.

Genexa's Lack of Motivation to Combine and Reasonable Expectation of Success Arguments Fail

The Crux of Genexa's Arguments: An Allegedly Incorrectly Presumed Viscosity for Agave Syrup

> The Petition is fundamentally flawed because of its reliance on an unsupported as well as incorrectly presumed viscosity for agave syrup. Obviousness

POR (Paper 20), 24

> The Petition has not done so here because it relies on the single erroneous 212 cP value for the presumed viscosity of agave syrup despite Petitioner's own cited evidence showing a materially higher viscosity of 2,560 cP. The Petition's reliance on this undisputable and dispositive error in asserting obviousness cannot be cured and the claims should be upheld as patentable on this basis alone. *See* 35 U.S.C. § 322(a)(3); *Magnum Oil Tools*, 829 F.3d at 1381

POR (Paper 20), 28

The Submitted Evidence Shows That Agave Syrup Can Have a Viscosity of 212cP

Patent Owner Response

The Petition has not done so here because it relies on the single erroneous 212 cP value for the presumed viscosity of agave syrup despite Petitioner's own cited evidence showing a materially higher viscosity of 2,560 cP. The Petition's reliance on this undisputable and dispositive error in asserting obviousness cannot be cured and the claims should be upheld as patentable on this basis alone. *See* 35 U.S.C. § 322(a)(3); *Magnum Oil Tools*, 829 F.3d at 1381

POR (Paper 20), 28

Soto 2011

Table 4. Physical characterization of syrups.

Parameter	Syrup	
	Frudex 55	Agave syrup
Soluble solids (°Brix)	70.0 ± 0.1[a]	70.0 ± 0.01[a]
Density (g/ml)	1.50 ± 0.005[a]	1.49 ± 0.003[a]
Water activity (aw)	0.702 ± 0.001[a]	0.699 ± 0.002[a]
Surface tension (dinas/cm)	50.50 ± 1.83[a]	45.30 ± 0.95[b]
Viscosity (mPa-s)	224 ± 3.9[a]	212 ± 3.5[b]
Color (a*/b*)	0.04 ± 0.001[a]	0.09 ± 0.003[b]

Different letters between columns of the same line indicate statistically significant differences ($p < 0.05$).

Ex. 1030, (cited in Reply (Paper 25), 10 fn 4 for the proposition that this reference "reports agave syrup with a viscosity of 212cP")

See also Pet. (Paper 2), 31, 57; Ex. 1003 (Crowley Decl.), ¶¶50, 52 (also noting that agave syrup has been reported to have a viscosity of 212cP)

The Petition Explains Agave Syrup Can Have Thicker or Thinner Consistency (i.e., Viscosity)

[1] Agave syrup can be processed as organic, natural or raw to a thicker or thinner consistency. *Id.* at [0005]. Thus, one can select the desired viscosity depending on the proposed use. Ex. 1003 at ¶52.

Pet. (Paper 2), 4 fn 1

Agave syrup or nectar is obtained by extracting agave juice and processing into a syrup. Ex. 1007 at 7, lns. 15-23. The product can be processed in an organic, natural, or raw state and can be of thicker or thinner consistency (viscosity). Ex. 1007 at 7, lns. 20-23.

Pet. (Paper 2), 22

The Petition Explains Agave Syrup Can Have Thicker or Thinner Consistency (i.e., Viscosity)

WO742

Agave nectar is obtained from the agave plant grown in arid regions, by extracting the agave juice therefrom and processing it into a syrup. See, for example, U.S. Pat. No. 5,846,333 of Partida et al., the disclosure of which is incorporated herein by reference. Commercially, other names for Agave nectar have been "Sweetener" or "Syrup" as well as other similar descriptive or extension names. However, it is generally considered a syrup-like product which can be processed as an organic, natural, or raw state. It can be light to dark in color, thicker or thinner in consistency (viscosity), and even made into powder or crystals if dehydrated totally.

Ex. 1007, 7:15-23 (cited on page 22 of the Petition)

Soto 2011

Table 4. Physical characterization of syrups.

Parameter	Syrup	
	Frudex 55	Agave syrup
Soluble solids (°Brix)	70.0 ± 0.1[a]	70.0 ± 0.01[a]
Density (g/ml)	1.50 ± 0.005[a]	1.49 ± 0.003[a]
Water activity (aw)	0.702 ± 0.001[a]	0.699 ± 0.002[a]
Surface tension (dinas/cm)	50.50 ± 1.83[a]	45.30 ± 0.95[b]
Viscosity (mPa-s)	224 ± 3.9[a]	212 ± 3.5[b]
Color (a*/b*)	0.04 ± 0.001[a]	0.09 ± 0.003[b]

Different letters between columns of the same line indicate statistically significant differences ($p < 0.05$).

Ex. 1030, (cited in Reply (Paper 25), 10 fn 4 for the proposition that this reference "reports agave syrup with a viscosity of 212cP")*

Vera-Guzmán 2011

***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.

Ex. 1031, 1 (cited on p. 1 of POR and in Ex. 1003 at ¶52*)

*Ex. 1003 (Crowley Decl.), ¶52 also notes that "[t]he viscosity of agave syrup is reported to be around 212mPa-S, or 212cP"

Dr. Crowley Explains That Agave Syrup Can Have Other Viscosities

A POSITA would have also known that there are different agave plant species (*Agave tequilina, Agave salmiana*) from which syrups can be obtained. A POSITA would have also known that syrups with different colors (light, amber, dark) and consistencies can be obtained from agave plants, depending on the means and degree of processing of the plant.

Ex. 1003, ¶93

WO742 further notes that "[a]gave syrup or agave nectar began appearing on health food store shelves in the early 2000s" and "agave syrup, also known as agave nectar, is a sweetener produced in Mexico from the *Agave americana plant*… [and] is similar to honey in color and texture, but it is less viscous and flows more easily." *Id.*, at p. 7, lns. 6-10. It also notes 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), and can be dehydrated and made into a power or crystals. *Id.*, at p. 7, lns. 15-23.

Ex. 1003, ¶68

See Pet. (Paper 2), 14-15; Ex. 1003 (Crowley Decl.), ¶¶50-52

Patent Owner's Focus on the Viscosity of Agave Syrup is a Red Herring

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.

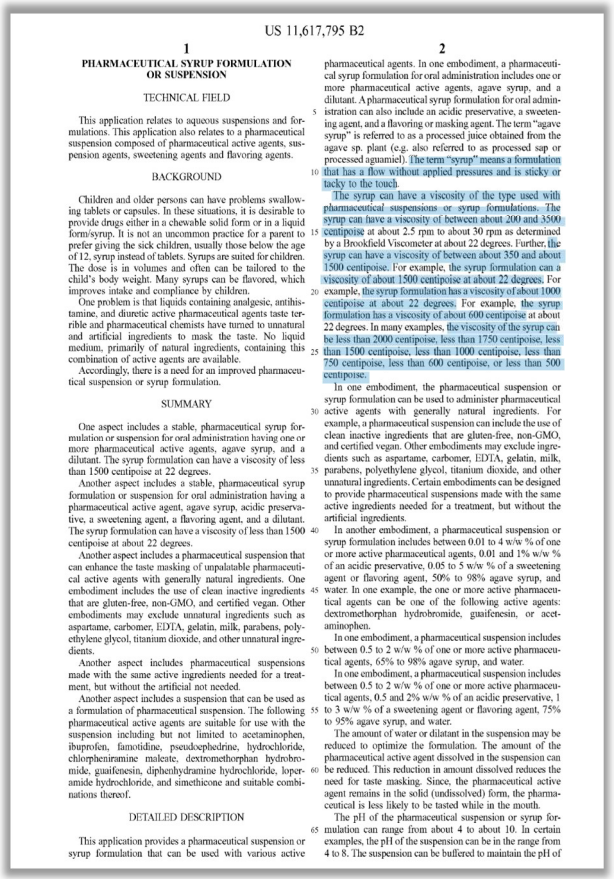
Ex. 1001, claims 1-4

The claims do not recite a viscosity for the agave syrup

Unlike in *Magnum Oil Tools*, this miscitation did not deprive Genexa of the opportunity to respond to the substantive obviousness arguments clearly articulated in the Petition. Moreover, none of these arguments even relied on a specific viscosity of agave syrup because the relevant viscosity is that of the formulation—not the agave syrup component only.

See Reply (Paper 25), 10

The ’795 Patent Only Discusses Acceptable Viscosities for the Final Syrup Formulation



US 11,617,795 B2

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PHARMACEUTICAL SYRUP FORMULATION OR SUSPENSION

TECHNICAL FIELD

This application relates to aqueous suspensions and formulations. This application also relates to a pharmaceutical suspension composed of pharmaceutical active agents, suspension agents, sweetening agents and flavoring agents.

BACKGROUND

Children and older persons can have problems swallowing tablets or capsules. In these situations, it is desirable to provide drugs either in a chewable solid form or in a liquid form/syrup. It is not an uncommon practice for a parent to prefer giving the sick children, usually those below the age of 12, syrup instead of tablets. Syrups are suited for children. The dose is in volumes and often can be tailored to the child's body weight. Many syrups can be flavored, which improves intake and compliance by children.

One problem is that liquids containing analgesic, antihistamine, and diuretic active pharmaceutical agents taste terrible and pharmaceutical chemists have turned to unnatural and artificial ingredients to mask the taste. No liquid medium, primarily of natural ingredients, containing this combination of active agents are available.

Accordingly, there is a need for an improved pharmaceutical suspension or syrup formulation.

SUMMARY

One aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having one or more pharmaceutical active agents, agave syrup, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at 22 degrees.

Another aspect includes a stable, pharmaceutical syrup formulation or suspension for oral administration having a pharmaceutical active agent, agave syrup, acidic preservative, a sweetening agent, a flavoring agent, and a dilutant. The syrup formulation can have a viscosity of less than 1500 centipoise at about 22 degrees.

Another aspect includes a pharmaceutical suspension that can enhance the taste masking of unpalatable pharmaceutical active agents with generally natural ingredients. One embodiment includes the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan. Other embodiments may exclude unnatural ingredients such as aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other unnatural ingredients.

Another aspect includes pharmaceutical suspensions made with the same active ingredients needed for a treatment, but without the artificial not needed.

Another aspect includes a suspension that can be used as a formulation of pharmaceutical suspension. The following pharmaceutical active agents are suitable for use with the suspension including but not limited to acetaminophen, ibuprofen, famotidine, pseudoephedrine, hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide, guaifenesin, diphenhydramine hydrochloride, loperamide hydrochloride, and simethicone and suitable combinations thereof.

DETAILED DESCRIPTION

This application provides a pharmaceutical suspension or syrup formulation that can be used with various active

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pharmaceutical agents. In one embodiment, a pharmaceutical syrup formulation for oral administration includes one or more pharmaceutical active agents, agave syrup, and a dilutant. A pharmaceutical syrup formulation for oral administration can also include an acidic preservative, a sweetening agent, and a flavoring or masking agent. The term "agave syrup" is referred to as a processed juice obtained from the agave sp. plant (e.g. also referred to as processed sap or processed aguamiel). The term "syrup" means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations. The 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. Further, the syrup can have a viscosity of between about 350 and about 1500 centipoise. For example, the syrup formulation can a viscosity of about 1500 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 1000 centipoise at about 22 degrees. In many examples, the viscosity of the syrup can be 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.

In one embodiment, the pharmaceutical suspension or syrup formulation can be used to administer pharmaceutical active agents with generally natural ingredients. For example, a pharmaceutical suspension can include the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan. Other embodiments may exclude ingredients such as aspartame, carbomer, EDTA, gelatin, milk, parabens, polyethylene glycol, titanium dioxide, and other unnatural ingredients. Certain embodiments can be designed to provide pharmaceutical suspensions made with the same active ingredients needed for a treatment, but without the artificial ingredients.

In another embodiment, a pharmaceutical suspension or syrup formulation includes between 0.01 to 4 w/w % of one or more active pharmaceutical agents, 0.01 and 1% w/w % of an acidic preservative, 0.05 to 5 w/w % of a sweetening agent or flavoring agent, 50% to 98% agave syrup, and water. In one example, the one or more active pharmaceutical agents can be one of the following active agents: dextromethorphan hydrobromide, guaifenesin, or acetaminophen.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 65% to 98% agave syrup, and water.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 0.5 and 2% w/w % of an acidic preservative, 1 to 3 w/w % of a sweetening agent or flavoring agent, 75% to 95% agave syrup, and water.

The amount of water or dilatant in the suspension may be reduced to optimize the formulation. The amount of the pharmaceutical active agent dissolved in the suspension can be reduced. This reduction in amount dissolved reduces the need for taste masking. Since, the pharmaceutical active agent remains in the solid (undissolved) form, the pharmaceutical is less likely to be tasted while in the mouth.

The pH of the pharmaceutical suspension or syrup formulation can range from about 4 to about 10. In certain examples, the pH of the suspension can be in the range from 4 to 8. The suspension can be buffered to maintain the pH of

> The term "syrup" means a formulation that has a flow without applied pressures and is sticky or tacky to the touch.

> The syrup can have a viscosity of the type used with pharmaceutical suspensions or syrup formulations. The 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. Further, the syrup can have a viscosity of between about 350 and about 1500 centipoise. For example, the syrup formulation can a viscosity of about 1500 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 1000 centipoise at about 22 degrees. For example, the syrup formulation has a viscosity of about 600 centipoise at about 22 degrees. In many examples, the viscosity of the syrup can be 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.

Ex. 1001, 2: 9-27

See Pet. (Paper 2), 14-16;Ex. 1003 (Crowley Decl.), ¶¶ 28, 93-94; Reply (Paper 25), 10

WO133 and the '4666 Patent Disclose the Independent Claims' Viscosity Limitations

Patent Owner Response

The Petition is fundamentally flawed because of its reliance on an unsupported as well as incorrectly presumed viscosity for agave syrup. Obviousness Grounds 1 and 2 in the Petition are entirely premised on the conclusory expert statements that "[t]he viscosity of agave syrup ***is reported to be about 212 centipoise***. . . . Ex. 1031, at p. 1" (Ex. 1003, ¶52 (emphasis added)) and "[a]s I

POR (Paper 20), 24

Petition

The viscosity of agave syrup has been reported to be about 212 centipoise. Ex. 1003 at ¶ 52. Thus, a person of ordinary skill in the art would understand that the formulation disclosed in Example 1 of FR458, which is largely made up of agave syrup, may have a viscosity less than 1500 centipoise. Ex. 1003 at ¶ 119. As both the '4666 Patent and WO133 disclose appropriate viscosity ranges for an oral formulation with an analgesic, it is unnecessary for the Board to conclude that Example 1 of the FR458 meets this limitation. The' 4666 patent discloses a viscosity range measured at 20° by a Brookfield Synchro-Lectric viscometer of 1000 to 3000 centipoise.[15] Ex. 1005 at col. 4, lns. 9-17. Claim 11 lowers the lower viscosity limit from 1000 to 100 centipoise. *Id.*, at col. 6, lns. 66-67. WO133 teaches a tighter viscosity range of 200 to 900 centipoise for its oral analgesic formulation.[16] Ex. 1006 at [8, lns. 1-3].

Pet. (Paper 2), 31

See also Pet. (Paper 2), 57; Institution Decision (Paper 8) at 24-25; Reply (Paper 25), 10-12

WO133 and the '4666 Patent Also Disclose the Dependent Claims' Viscosity Limitations

Patent Owner Response

The Petition is fundamentally flawed because of its reliance on an unsupported as well as incorrectly presumed viscosity for agave syrup. Obviousness Grounds 1 and 2 in the Petition are entirely premised on the conclusory expert statements that "[t]he viscosity of agave syrup ***is reported to be about 212 centipoise***. . . . Ex. 1031, at p. 1" (Ex. 1003, ¶52 (emphasis added)) and "[a]s I

POR (Paper 20), 24

Petition

Claim 2 narrows the viscosity range to less than 1000 centipoise. Claim 3 narrows the range further to less than 750 centipoise, while claim 4 narrows further to less than 600 centipoise. Each of these ranges is disclosed in the references relied upon here. Claim 11 of the '4666 patent discloses a viscosity range from 100 to 3000 centipoise. Ex. 1005 at col. 6, lns. 66-67. WO133 teaches a tighter viscosity range of 200 to 900 centipoise for its oral analgesic formulation. Ex. 1006 at 7, ln. 27-8, ln. 4. As both teach viscosity below the upper limit required by claims 2, 3, and 4, a person of ordinary skill in the art would conclude that the presence of these limitations do not save the claims from an obviousness conclusion. Ex. 1003 at ¶¶ 114-116, 132-133.

Pet. (Paper 2), 34

See also Pet. (Paper 2), 60; Ex. 1003 (Crowley Decl.), ¶¶ 132-133, 227-228; Reply (Paper 25), 10-12

Dr. Berkland Asserts that a POSITA Would Expect Example 1 of FR458 to Have a Viscosity <200 cP If Made with 212cP Agave Syrup

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

Ex. 2009 (Berkland Decl.), ¶150 (cited in Reply (Paper 25), 11, 11 fn. 5)

Example 1

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

The xanthan gum and the agar-agar are mixed with the glycerin to obtain Solution A. The paracetamol is suspended 225 [sic] in the syrup to obtain Solution B. Solution A is added to Solution B and mixed well. The water is topped up to 100 ml and everything is mixed together. The preparation is placed in vials.

Ex. 1004, 8: Example 1, 199-204 (cited in the Petition at p. 32)

See also Reply (Paper 25), 1

Patent Owner's Expert Asserts that The Formulation Cited in Example 1 of FR458 Would Have a Viscosity <200cP

*"[I]t is well settled that 'a disclosure that anticipates under §102 also renders the claim invalid under §103, for '**anticipation is the epitome of obviousness.**'"*

Realtime Data, LLC v. Iancu, 912 F.3d 1368, 1373 (Fed. Cir. 2019)

See also Reply (Paper 25), 1

Dr. Berkland's Testimony is Inconsistent

Dr. Berkland's Written Testimony

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]

Ex. 2009 (Berkland Decl.), ¶150

Example 1

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

Ex. 1004, 8

Dr. Berkland's Oral Testimony

Q. And depending on the agave syrup that is used, would you expect that the formulation of Example 1 of 1004 may have formulation viscosity below 1500 centipoise?

A. We don't know without making assumptions.

Q. What assumptions would you have to make?

A. There would have to be disclosure of the agave syrup, I see other ingredients included here, gums and agar, A-G-A-R, and I'm just not entirely sure how these in combination contribute to the viscosity, there's no disclosure.

Ex. 1051, 168:15-169:7

Reply (Paper 25), 11, 11 fn. 5

Genexa Argues that the Non-Overlapping Viscosities of the '4666 Patent and WO133 "Teach Away" from the Combination

A POSA would not have been motivated to combine the 1000-3000 cP range of the '4666 patent with the 200-900 cP range of WO133 or have reasonably expected success in doing so because they are wholly distinct and non-overlapping ranges. (Ex. 2009, ¶¶147-50.) Why would a POSA combine two different and non-overlapping viscosity ranges in these references? The answer is simple. A POSA would not make any such combination. (*Id.*) Indeed, Petitioner makes no attempt to address the obvious disconnect between the viscosity ranges in the '4666 patent (1000-3000 cP) and WO133 (200-900 cP) asserted in the Petition.

POR (Paper 20), 34-35

Reply (Paper 25), 9-10

The Disclosed Viscosities of the '4666 Patent and WO133 Overlap

The '4666 Patent

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, col.4, lns. 9-17 (cited in Petition at pages 31, 58 and Ex. 1003 at paras 119, 168, 191*)

11. The syrup of claim 7 wherein the viscosity is about 100 to 3000 centipoise at 20° C.

Ex. 1005, claim 11 (cited in Petition at pages 31, 34, 52-53, 58, 60)

WO133

about 1.25 to about 1.32 g/ml. The viscosity of the acetaminophen composition generally ranges from about 200-900 centipoise, preferably from about 300-700 centipoise.

Ex. 1006, 8:1-3 (cited in Petition at pages 31, 58)

Moreover, a lack of overlap between the viscosity ranges taught by WO133 and the '4666 Patent would not affect the 2-reference combinations

Reply (Paper 25), 9

* These paragraphs of Ex. 1003 are cited at pages 31-32, 45 and 52-53

Claim 11 Does Not Include an "Apparent Error" that a POSITA Would "Mentally Disregard"

Genexa Argues

The Petition relies on the '4666 Patent as purportedly teaching a POSA a viscosity range of 100-3000 centipoise even though such recitation is an obvious error. (Ex. 2009, ¶¶122-33.)

Because a POSA would readily recognize the nature of the error within the '4666 Patent, as well as the internal inconsistency, the Board should disregard Petitioner's assertion that the '4666 patent discloses a viscosity of 100-3000 centipoise since such a typographical error would have been disregarded. *See LG Elecs*, 39 F.4th at 1365 ("Because substantial evidence supports the Board's finding that prior art disclosure critical to both of LG's petitions for *inter partes* review was an apparent error that would have been disregarded or corrected by a person of ordinary skill in the art, we affirm.").

POR (Paper 20), 30-31

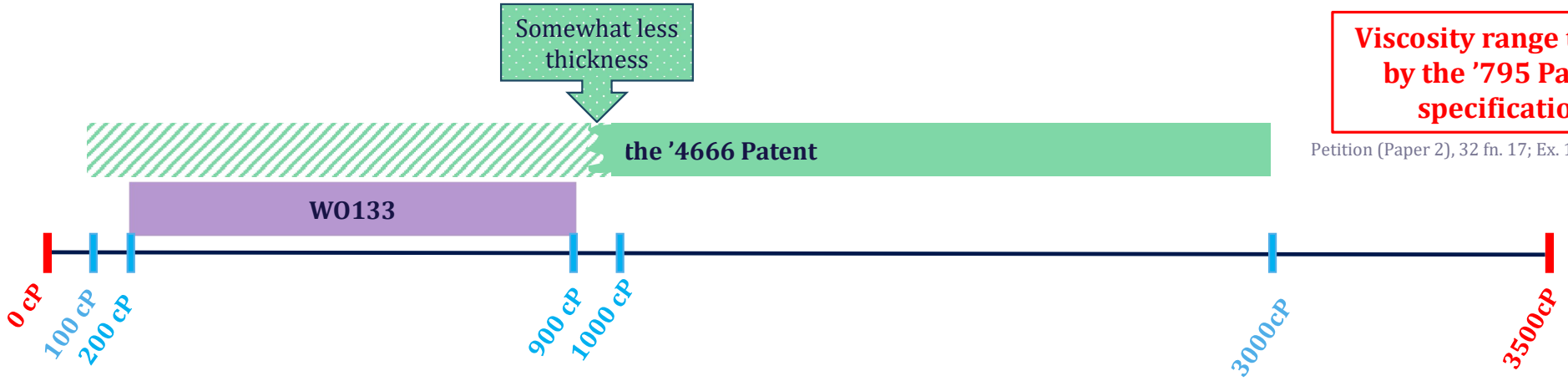
However, the '4666 Patent:

- Describes 1000-3000cP as a ***preferred*** range. (Cited at para 168 of Ex 1003*)
- States "[f]inished products of *somewhat* ***less thickness"*** are acceptable. (Cited at para 168 of Ex. 1003* and in Reply at page 13, fn. 9)
- Includes independent claims without viscosity requirements. (Cited in Reply at page 13, fn. 9)
- Recites a very simple stabilized formulation in claim 7 that allows ingredients with viscosities below 1000cP, upon which claim 11 depends. (Cited in Reply at page 13, fn. 9)

Patent Owner's "lack of overlap" arguments are predicated on ignoring the explicit disclosure of the '4666 Patent and accepting that the 100-3000cP disclosure is an obvious error.

* Para 168 of Ex. 1003 is cited in the Pet. (Paper 2) at 44-45

Even if the '4666 Patent's Viscosity is ~1000-3000 cP that Aligns with "Viscosities of the type used with pharmaceutical suspensions or syrup formulations"



Viscosity range taught by the '795 Patent specification

Petition (Paper 2), 32 fn. 17; Ex. 1001, 2: 13-27

Exhibit	Oral Formulation Viscosity Range
The '4666 Patent (Ex. 1005)	100 to 3000 cP
WO133 (Ex. 1006)	200 to 900 cP
Valinoti 2016 (Ex. 1036)	20 to 1780 cP
Neves 2010 (Ex. 1046)	2.8 to 412.3 cP
Subramaniam (Ex. 2020)	307.33-2408.33cP

Viscosity ranges taught by the prior art cited in the Grounds

See Ex. 1005, 4:10-11, claim 11, Ex. 1006, 8:1-3, Ex. 1036, abstract, table 2, Ex. 1046, abstract, table 4, Ex. 2020, abstract, table 1, which are cited in Pet., (Paper 2), 7 (citing Ex. 1001, Ex. 1003, Ex. 1005 and Ex. 1006); Ex. 1003 (Crowley Decl.), ¶28 (citing Ex. 1001), ¶58 (citing Ex. 1036); and Reply (Paper 25) at 8 and 15.

Reply (Paper 25), 15

Dr. Crowley's Statements Regarding Suspensions That Are Considered "Readily Pourable" Do Not "Teach Away"

Petitioner's expert further argued against any viscosity higher than those that are considered "readily pourable with "***a viscosity in the range of 20 to 150 cP***" for acetaminophen formulations because "increasing the viscosity of a suspension formulation has been show to impair the dissolution characteristics of immediate release acetaminophen." (Ex. 1003, ¶59 (emphasis added).) Petitioner's expert also argued that "[w]ith respect to suspensions for oral administration, having a higher viscosity is generally not desirable." (*Id.*) Thus, Petitioner's own expert testimony demonstrates a motivation *not to combine* the acetaminophen formulation of FR458-Example 1 with the 1000-3000 cP range of the '4666 patent and the 200-900 cP range of WO133 since by his own admission doing so would yield bad results (i.e., impairing the dissolution characteristics of the acetaminophen) and generally undesirable higher viscosity. (Ex. 2009, ¶148.)

POR (Paper 20), 45-46

- "Readily pourable" is not a claim limitation (Reply (Paper 25) at pp. 8-9)
- These are statements made in Dr. Crowley's declaration and are NOT statements present in the prior art references cited for obviousness in Grounds 1 and 2, so they cannot "teach away" from the viscosity limitations of the claimed invention (Reply (Paper 25) at p. 8)

Reply (Paper 25), 8, 8 fn. 3, 15

Moreover, Dr. Crowley Never Argued Against Viscosities Higher than 20-150cP

What Dr. Crowley actually said:

59. With respect to suspensions for oral administration, however, having a higher viscosity is generally not desirable. One drawback of having too high a viscosity in a suspension formulation is that it can make the formulation difficult to pour. Ex. 1012, at p. 768. Generally, suspensions having a viscosity in the range of 20 to 150 cP are considered readily pourable. Ex. 1014, at pp. 1489-1490. Additionally, increasing the viscosity of a suspension formulation has been shown to impair the dissolution characteristics of immediate release acetaminophen. Ex. 1013, at p. 1537.

Ex. 1003 (Crowley Decl.), ¶59 (cited in the Petition at pages 7 and 31.)

- He repeatedly states (and the prior art confirms) that oral formulations with viscosities more than ***10x greater*** than ***150cP*** are pourable and drinkable. (Ex. 1003, ¶¶28, 58, 216, 227, which are cited in the Petition at pages 31 and 57 and in the Reply (Paper 25) at pp. 8, fn. 3)
- He cites to p. 768 of Ex. 1012, which teaches that "***very high viscosity***" is generally not desirable because it pours with difficult and is difficult to redisperse. (Ex. 1003, ¶59*)
- He cites to p. 1537 of Ex. 1013, which teaches that viscosities of ***3650cP and 4380cP*** impair the dissolution characteristics of ***immediate release acetaminophen*** (Ex. 1003, ¶59*)

Cited in the Petition (Paper 2), at p. 31 and the Reply (Paper 25) at p. 8, p. 8 fn. 3, 15

The Prior Art Discloses All of the Claim Limitations That Genexa Challenges

Genexa Does Not Dispute

- June 8, 2021, is the earliest possible priority date to which the '795 Patent is entitled.
- FR458, the '4666 Patent, WO133 and WO742 are prior art to the '795 Patent.
- All the limitations of independent claims 1, 7 and 18 are disclosed by the prior art cited in the Petition except for the viscosity limitations.*
- The limitations of dependent claims 10-12, 14, 16 and 22-23 are disclosed by the prior art cited in the Petition.

* Genexa states that "none of the proposed combinations disclose viscosities that meet the claim limitations." See POR at 3. But Genexa never explains how the individual teachings of the '4666 patent and WO133 do not disclose the claimed viscosity ranges.

Genexa Only Disputes

- The viscosity limitations are disclosed by the prior art cited in the Petition.*
  - Claim 11 of the '4666 Patent discloses a formulation viscosity range of 100-3000cP.
- The limitations of dependent claims are disclosed by the prior art cited in the Petition . 2-6, 8-9, 19-21, and 24 are disclosed by the prior art cited in the Petition.

* Genexa states that "none of the proposed combinations disclose viscosities that meet the claim limitations." See POR at 3. But Genexa never explains how the individual teachings of the '4666 patent and WO133 do not disclose the claimed viscosity ranges.

The Viscosity Limitations Are All Disclosed

Claims 1-24

The Overlapping Viscosity Ranges Taught By the Prior Art and the '795 Patent Created a Presumption of Obviousness

"If the relevant comparison between a disputed claim limitation and the prior art pertains to a range of overlapping values, 'we and our predecessor courts have consistently held that even a slight overlap in the range establishes a prima facie case of obviousness."

Genentech, Inc. v. Hospira, Inc. 946 F.3d 1333, 1341 (Fed. Cir. 2020)

Reply (Paper 25), 13-14

The ’4666 Patent Discloses Oral Formulations That Meet All of the Viscosity Limitations of the Challenged Claims

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.

11. The syrup of claim 7 wherein the viscosity is about 100 to 3000 centipoise at 20° C.

Ex. 1005, 4:9-17, claim 11

Ranges overlap?

Claim 1: “…the syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees…” ☑

Claim 2: “…the syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees…” ☑

Claim 3: “…the syrup formulation has a viscosity of less than 750 centipoise at about 22 degrees…” ☑

Claim 4: “…the syrup formulation has a viscosity of less than 600 centipoise at about 22 degrees…” ☑

Claim 15: “…the composition has a viscosity from about 1500 centipoise to about 400 centipoise at about 22 degrees…” ☑

Ex. 1001, claims 1-4, 15

Pet. (Paper 2), 25, 31, 34, 44, 52-53, 58, 60, 66; Ex. 1003 (Crowley Decl.), ¶¶74, 119, 132, 167-169, 191;Reply (Paper 25), 12-15

WO133 Discloses Oral Formulations That Meet All of the Viscosity Limitations of the Challenged Claims

> The viscosity of the acetaminophen composition generally ranges from about 200-900 centipoise, preferably from about 300-700 centipoise.

Ex. 1006, 8:1-3

	Ranges overlap?
Claim 1: "…the syrup formulation has a viscosity of less than 1500 centipoise at about 22 degrees…"	☑
Claim 2: "…the syrup formulation has a viscosity of less than 1000 centipoise at about 22 degrees…"	☑
Claim 3: "…the syrup formulation has a viscosity of less than 750 centipoise at about 22 degrees…"	☑
Claim 4: "…the syrup formulation has a viscosity of less than 600 centipoise at about 22 degrees…"	☑
Claim 15: "…the composition has a viscosity from about 1500 centipoise to about 400 centipoise at about 22 degrees…"	☑

Ex. 1001, claims 1-4, 15

Pet. (Paper 2), 26, 31, 34, 44, 52-53, 58, 60, 66; Ex. 1003 (Crowley Decl.), ¶¶68, 80, 119, 132, 167-169, 191; Reply (Paper 25), 12-15

The Presumption that the Viscosity Ranges Claimed By the '795 Are Obvious Has Not Been Rebutted

Genexa has failed to show:

"teaching away, unexpected results or criticality, or other pertinent objective indicia indicating that the overlapping range would not have been obvious in light of that prior art."

E.I. DuPont de Nemours & Company v. Synvina C.V., 904 F.3d 996, 1008 (C.A.Fed., 2018)

The Acetaminophen Concentration Ranges Are Disclosed

Claims 5, 6 and 8

Claims 5, 6 & 8 of the ’795 Patent

5.	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup.
6.	The pharmaceutical syrup formulation of claim 1, wherein 0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup
8.	The pharmaceutical syrup formulation of claim 7, wherein the acetaminophen is between 0.01 to 2% of the formulation weight.

Ex. 1001, claims 5-6, 8

WO742 Discloses An Acetaminophen Concentration That Fall Within the Acetaminophen Concentration Ranges of Claims 5 & 6

EXAMPLE IX. Liquid Cough Composition Ingredients	Amount/15 ml Dose:
Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

The formulation in Example IX includes 1g per 100mL of acetaminophen

Falls within range?

Claim 5: "wherein 0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup" ☑

Claim 6: "wherein 0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup" ☑

Pet. (Paper 2), 60-61, 64; Ex. 1003 (Crowley Decl.), ¶¶229-232, 245-246; Reply (Paper 25), 16-18, 16 fn.1

FR458 and WO133 Teach Acetaminophen Concentration Ranges That Overlap With Those of Claims 5, 6 and 8

FR458

The active pharmaceutical ingredients that may be incorporated must be compatible with the other essential ingredients and compatible in combination with other active ingredients or compounds and may be present in concentrations ranging from about 0.01% to about 90%, preferably from about 0.1% to about 75%, more preferably from about 1.0% to about 50% and even more preferably from about 1.0% to about 25%.

Ex. 1004, 3: 78-85

Falls within range?

Claim 5: "wherein 0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup" ✓

Claim 6: "wherein 0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup" ✓

Claim 8: "wherein the acetaminophen is between 0.01 to 2% of the formulation by weight" ✓

WO133

The invention provides an acetaminophen composition in taste-masked form, suitable for oral administration, containing acetaminophen in an aqueous medium. The acetaminophen composition contains acetaminophen in an amount of up to about 10% by weight, preferably from about 2 to about 8% by weight, in an aqueous medium.

Ex. 1005, 2:14-19

Falls within range?

Claim 5: "wherein 0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup" ✓

Claim 6: "wherein 0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup" ✓

Claim 8: "wherein the acetaminophen is between 0.01 to 2% of the formulation by weight" ✓

Ex. 1001, claim 5-6, 8

Pet. (Paper 2), 34-38, 42; Ex. 1003 (Crowley Decl.), ¶¶134-137, 153-154; Reply (Paper 25), 16-18

The Overlapping Viscosity Ranges Taught By the Prior Art and the '795 Patent Created a Presumption of Obviousness

"If the relevant comparison between a disputed claim limitation and the prior art pertains to a range of overlapping values, 'we and our predecessor courts have consistently held that even a slight overlap in the range establishes a prima facie case of obviousness."

Genentech, Inc. v. Hospira, Inc. 946 F.3d 1333, 1341 (Fed. Cir. 2020)

Reply (Paper 25), 13-14

Genexa Incorrectly Argues That The Ranges Disclosed by FR458 and WO133 Are So Broad That Overlapping Ranges Do Not Apply

Claims 5, 6, and 8 recite concentrations of the acetaminophen in 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, 5:51-56, 6:6-8.) Petitioner contends that the proposed combination of Ground 1 allegedly satisfies these dependent concentration limitations based on FR458 teaching that "the API can be between 0.01 to about 90% of the formulation" and WO133 teaching a concentration of "up to about 10% by weight." (Pet. at 42; *see also id.* at 34-35.)

Where, as here the disclosed range is "so broad as to encompass a very large number of possible distinct compositions," overlapping ranges do not apply. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) (citing *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003)).

POR (Paper 20), 65

***Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.* does not apply here. In that case, the court found no *prima facie* case of obviousness due to the unusually broad ranges in the prior art, which encompassed many distinct compositions* requiring nonobvious invention.**

*The disclosed prior art range included 68,000 truncated protein variants made up of 2,332 amino acids, which differed in terms of the size and location of the amino acid deletions, and the degree of permitted amino acid substitutions

Reply (Paper 25), 17-18, 18 fn. 12

Genexa Ignores the Narrower API Concentration Ranges Taught by FR458 and WO133

Patent Owner Response

Claims 5, 6, and 8 recite concentrations of the acetaminophen in 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, 5:51-56, 6:6-8.) Petitioner contends that the proposed combination of Ground 1 allegedly satisfies these dependent concentration limitations based on FR458 teaching that "the API can be between 0.01 to about 90% of the formulation" and WO133 teaching a concentration of "up to about 10% by weight." (Pet. at 42; *see also id.* at 34-35.) Where, as here the disclosed range is "so broad as to encompass a very large number of possible distinct compositions," overlapping ranges do not apply. *Genetics Inst.,*

POR (Paper 20), 65

FR458

The active pharmaceutical ingredients that may be incorporated must be compatible with the other essential ingredients and compatible in combination with other active ingredients or compounds and may be present in concentrations ranging from about 0.01% to about 90%, preferably from about 0.1% to about 75%, more preferably from about 1.0% to about 50% and even more preferably from about 1.0% to about 25%.

Ex. 1004, 3:78-85

WO133

The invention provides an acetaminophen composition in taste-masked form, suitable for oral administration, containing acetaminophen in an aqueous medium. The acetaminophen composition contains acetaminophen in an amount of up to about 10% by weight, preferably from about 2 to about 8% by weight, in an aqueous medium.

Ex. 1006, 2:14-19

Pet. (Paper 2), 34-35, 38; Ex. 1003 (Crowley Decl.), ¶136; Reply (Paper 25), 17

Genexa Also Ignores that the Claimed Acetaminophen Ranges Are Very Broad Themselves

Claim	Acetaminophen concentration	Difference between upper and lower concentrations
5.	0.01 to 2 grams of acetaminophen is suspended per 100mL of the syrup	200x
6.	0.01 to 1 grams of acetaminophen is suspended per 100mL of the syrup	100x
8.	between 0.01 to 2% of the formulation weight.	200x

Ex. 1001, claims 5-6, 8

Pet. (Paper 2), 34-36; Ex. 1003 (Crowley Decl.), ¶121 fn. 27; Reply (Paper 25), 18

A POSITA Would Understand that Practical Limits Exist for the Acetaminophen Concentration in an Oral Formulation

Desired Therapeutic Dose of API (mg)	Concentration of API in the Formulation (g/100 mL)	Volume Required to Achieve the API Therapeutic Dose (teaspoons=mL)
120 mg	2.4 g/100 mL[18]	1 teaspoon = 5 mL
120 mg	1.2 g/100 mL	2 teaspoons = 10 mL
120 mg	0.8 g/100 mL	3 teaspoons = 15 mL
120 mg	0.01 g/100 mL	240 teaspoons = 1,200 mL or 1.2 Liters

Pet. (Paper 2), 36

Pet. (Paper 2), 35-36; Ex. 1003 (Crowley Decl.), ¶134 (Table 2).

The Claimed Agave Syrup Concentrations Are Obvious Design Choices

Claims 13 and 24

Claims 13 and 24 of the ’795 Patent

13.	The pharmaceutical syrup formulation of claim 7, wherein the agave syrup is about 95% of the formulation by weight.
24.	The pharmaceutical syrup formulation of claim 18, wherein the agave syrup is about 95% of the formulation by weight.

Ex. 1001, claims 13, 24

The Amount of Agave Syrup is a Design Choice that is Within a POSITA's Skill Set

162. A person of ordinary skill in the art would have understood from the disclosure of FR458 that the formulations of the invention can include different amounts of agave syrup (Examples 1 – 4 disclose four formulations that all contain agave syrup but the syrup makes up different percentages of each formulation's final weight). Therefore, a person of ordinary skill in the art would have understood that the formulations disclosed by FR458 could include formulations that contain about 95% agave syrup by weight.

Ex. 1003, ¶162

164. Therefore, FR458, in combination with the general knowledge of a person skilled in the art described in the '580 Publ., discloses "wherein the agave syrup is about 95% of the formulation by weight." In my opinion, claim 13 is not patentable because it would have been obvious to a person of ordinary skill in the art.

Ex. 1003, ¶164

Heyer 2009

[0023] Traditional natural and artificial sweeteners are added to most food products and medicines. These sweeteners can range from 2% to 98% of their total content.

Ex. 1008, [0023]

Pet. (Paper 2), 4 (citing Ex. 1008), 27 (citing Ex. 1008), 43-44 (citing Ex. 1003); Reply (Paper 25), 21-22, 22 fn. 13 (citing Ex. 1003 and Ex. 1008)

Patent Owner Wrongly Argues that Petition Makes a Conclusory Assertion "About 95%" Agave Syrup Being a Design Choice

formulation by weight. (Ex. 2009, ¶163.) Petitioner makes the conclusory assertion that "the amount of agave syrup to use in the formulation is a design choice within the general knowledge of the skilled artisan" and that the claim is allegedly satisfied because a prior art reference teaches that "sweeteners" can be added to "food products and medicines" in a "range from 2% to 98% of their total content." (Pet. at 43.) This range is so broad it cannot support obviousness. *See Genetics Inst.*, 655 F.3d at 1306. Likewise, Petitioner's conclusory assertion of a "design choice" cannot support obviousness. *See Magnum Oil Tools*, 829 F.3d at 1380. Finally, Petition again fails to address the claims as a whole by failing to provide any discussion regarding a motivation or reasonable expectation of success to make a "design choice" to modify FR458-Example 1 or how such a modification would also impact the viscosity of FR458-Example 1. (*See* Ex. 2009, ¶164.)

POR (Paper 20), 56

Claim 13 requires that the agave syrup make up about 95% of the formulation. A person of ordinary skill in the art would understand the amount of agave syrup to use in the formulation is a design choice within the general knowledge of the skilled artisan. Ex. 1003 at ¶¶ 161-162. Moreover, the '580 Publ. evidences the general knowledge of a person skilled in the art with regard to agave syrup concentrations by noting that "[t]raditional natural and artificial sweeteners are added to most food products and medicines. These sweeteners can range from 2% to 98% of their total content."[22] Ex. 1003 at [0023]; Ex. 1003 at ¶ 163. Thus, a person of ordinary skill in the art would conclude that this claim is unpatentable as obvious. Ex. 1003 at ¶ 164.

Pet. (Paper 2), 43

"About 95%" Agave Syrup per Formulation Weight Is an Obvious Design Choice

"[About 95% agave syrup per formulation weight] ***provides no novel or unexpected result.*** *[About 95% agave syrup] would be an obvious matter of design within the skill of the art... [U]se of [about 95% agave syrup] in the manner claimed is well known..."*

Application of Kuhle, 526 F.2d 553, 555 (Cust. & Pat.App. 1975)

Reply (Paper 25), 21-22

The ’795 Patent Does Not Teach Any Novel or Unexpected Result Related to “About 95%” Agave Syrup Per Formulation Weight

In another embodiment, a pharmaceutical suspension or syrup formulation includes between 0.01 to 4 w/w % of one or more active pharmaceutical agents, 0.01 and 1% w/w % of an acidic preservative, 0.05 to 5 w/w % of a sweetening agent or flavoring agent, 50% to 98% agave syrup, and water. In one example, the one or more active pharmaceutical agents can be one of the following active agents: dextromethorphan hydrobromide, guaifenesin, or acetaminophen.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 65% to 98% agave syrup, and water.

In one embodiment, a pharmaceutical suspension includes between 0.5 to 2 w/w % of one or more active pharmaceutical agents, 0.5 and 2% w/w % of an acidic preservative, 1 to 3 w/w % of a sweetening agent or flavoring agent, 75% to 95% agave syrup, and water.

Ex. 1001, 2:40-56

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, 5:10-19 (Example 1)

The ’795 Patent also does not specify the properties of the agave syrup used in its formulation, including its water content and viscosity.

Pet., (Paper 2), 7, 14-15, 51-52; Reply (Paper 25), 21-22, 22 fn. 13

The Claimed Diluent Concentration is Disclosed by the Prior Art

Claim 9

FR458, the '4666 and WO742 Each Teach Including Water in a Quantity Sufficient to Achieve a Desired Final Volume

A person of ordinary skill in the art would understand that amount of water is not critical, but merely serves to bring the formulation to the desired volume. Ex. 1003 at ¶ 247. That disclosure would include formulations where the water is about 5% by weight. Ex. 1003 at ¶ 247.

Pet. (Paper 2), 64

Pet., (Paper 2), 30, 64; Ex. 1003 (Crowley Decl.), ¶¶116-117, 247; Reply (Paper 25), 19-20

Genexa Argues that KinderFarms Fails to Justify Why a POSITA Would Alter FR458 and WO742's Examples to Achieve 5% Diluent

Claim 9 recites a further limitation to independent claim 7, "wherein the diluent is about 5% of the formulation by weight." (Ex. 1001, 6:9-11.) FR458-Example 1 is at least about 45% of the formulation by weight. (Ex. 2009, ¶160.) Petitioner makes the conclusory assertion that "[a] person of ordinary skill in the art would understand that the amount of water serves to bring the formulation to a desired volume and can be modified *within reason* without altering the effectiveness of the formulation" and that "this would include formulations where the water is about 5% by weight." (Pet. at 42-43.) But a change in FR458-Example 1 from over 45% water to 5% water would not be "within reason." (*See* Ex. 2009, ¶161.) FR458 already provides a final volume of 100 mL for FR458-Example 1 to achieve, at least in part, the desired concentration of acetaminophen. (*See id.*, ¶¶82-83.)

POR (Paper 25), 55

Reply (Paper 25), 19-20

A POSITA Would Have Understood the Advantage of Limiting the Amount of Diluent

The '795 Patent does not explain why including a diluent in the formulation of the invention in an amount that is about 5% of the formulation by weight is important (or inventive). However, a person of ordinary skill in the art would have understood from the disclosures of FR458 and the '4666 Patent (and WO133) that limiting the amount of diluent can help reduce the dissolution of the API in the composition, which is advantageous if the API is bitter or unpleasant-tasting when dissolved. Ex. 1006, p. 3, lns. 8-18.

Ex. 1003(Crowley Decl.), ¶155

Pet. (Paper 2), 42-43; Reply (Paper 25), 19-20

Claim 18's Formulation "Consisting Essentially Of" is Disclosed

Claim 18

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 wherein the acetaminophen is suspended in the syrup.

Ex. 1001, Claim 18

"Consisting Essentially Of" Includes Unlisted Ingredients that Do Not Affect the Basic and Novel Properties of the Invention

*"By using the term '**consisting essentially of**,' the drafter signals that the invention necessarily includes the listed ingredients and is **open to unlisted ingredients that do not materially affect the basic and novel properties of the invention**."*

AVX Corporation v. Greatbatch Ltd., IPR2014-01361, *3-*4 (PTAB Feb. 19, 2015) (citing *PPG Indus. V. Guardian Indus.,* 156 F.3d 1351, 1354 (Fed. Cir. 1998).

Pet. (Paper 2), 17, 48

The "Novel and Basic" Properties of the Invention Disclosed By the '795 Patent Are Unclear

The '795 Patent's specification offers few clues as to what may be the "novel and basic aspect" of the invention disclosed. As I previously explained in ¶ 98, the only statements in the '795 Patent specification that shed light on this are those which identify the problem of using "unnatural and artificial ingredients" to mask the taste of pharmaceutical liquids containing various drugs, including analgesics, and those which describe embodiments that include the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan, or those that exclude "unnatural ingredients." Ex. 1001, at 1: 21-24, 1:42-50. At most, a person of ordinary skill in the art may think that the "basic and novel aspect" of the formulations disclosed might be the lack of unnatural and artificial ingredients.

Ex. 1003 (Crowley Decl.), ¶179

Pet. (Paper 2), 17-19, 18 fn. 11-12, 49, 71; Ex. 1003 (Crowley Decl.), ¶¶ 98, 179

If the "Novel and Basic" Properties Require Excluding Unnatural and Artificial Ingredients, Then FR458 Teaches This

Example 1

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

Ex. 1004, 8

These ingredients do not materially affect the basic and novel properties of the invention of the '795 Patent

- **Xanthan gum:** Natural polysaccharide produced through fermentation of carbohydrates by *Xanthomonas campestris.* Used as a suspending agent and a viscosity increasing agent.
- **Agar agar:** Natural polysaccharide derived from algae. Used as a viscosity increasing agent.
- **Glycerin:** Occurs naturally in animal and vegetable fats and oils. Used as a sweetener and a viscosity agent.

Pet. (Paper 2), 49-50, 71; Ex. 1003 (Crowley Decl.), ¶¶ 179, 181 (citing Ex. 1029)

Claim 18 and its Dependent Claims are Indefinite

The Definiteness Requirement Applies to a "Consisting Essentially of" Claim

"Because the basic and novel properties of an invention are part of the construction of a claim containing the phrase 'consisting essentially of,' the Nautilus standard applies to the assessment of an invention's basic and novel properties. ***Accordingly, the construction of the basic and novel properties is governed by 35 U.S.C. § 112, ¶ 2 and the accompanying analysis from Nautilus."***

Horizon Pharma Ireland Limited v. Actavis Laboratories, UT, Inc., at *8 (D. N. J. Aug. 17, 2016).

Pet. (Paper 2), 70-72

The "Novel and Basic" Properties of the Claimed Invention Are Indefinite

The '795 Patent's specification offers few clues as to what may be the "novel and basic aspect" of the invention disclosed. As I previously explained in ¶ 98, the only statements in the '795 Patent specification that shed light on this are those which identify the problem of using "unnatural and artificial ingredients" to mask the taste of pharmaceutical liquids containing various drugs, including analgesics, and those which describe embodiments that include the use of clean inactive ingredients that are gluten-free, non-GMO, and certified vegan, or those that exclude "unnatural ingredients." Ex. 1001, at 1: 21-24, 1:42-50. At most, a person of ordinary skill in the art may think that the "basic and novel aspect" of the formulations disclosed might be the lack of unnatural and artificial ingredients.

Ex. 1003 (Crowley Decl.), ¶179

While one may argue that the formulations of claim 18 exclude unnatural and artificial ingredients, that is inconsistent with sections of the specification.

Flavoring agents also may be added to the pharmaceutical suspensions or syrup formulations to improve the palatability of the suspension. Examples of suitable flavoring agents include natural and artificial flavors such as mints (i.e., peppermint, etc.,), menthol, cinnamon, vanilla, artificial vanilla, chocolate, artificial chocolate, both natural and artificial fruit flavors (i.e., cherry, grape, orange, strawberry, etc.,) and combinations of two or more thereof. Flavoring

Ex. 1001, 3:64-4:3

Pet. (Paper 2), 7 (citing Ex. 1001), 17-19 (citing Ex. 1003), 18 fns. 11 and 12 (citing Ex. 1003), 49, and 71-72 (citing Ex. 1003); Ex. 1003 (Crowley Decl.), ¶¶ 98 (citing Ex. 1001), 179, 273

Patent Owner Has Not Provided Any Arguments Regarding Claim 18 or the Basic and Novel Properties of the Claimed Invention

> In this Response, Patent Owner has not made any arguments relating to the terms "palatable," "stable," or "consisting essentially of."

POR (Paper 20), 68

The specification and the Patent Owner's failure to explain what are the "the basic and novel properties of the invention" are is an admission that "consisting essentially of" does not meet the requirements of 35 U.S.C. §112(b)

Pet. (Paper 2), 71-72

Dr. Berkland's Testimony Should Be Given Less Weight

Dr. Berkland Has Failed to Consider the Scope of the Challenged Claims

Dr. Berkland's opinions should be given very little weight due to their unreliability. During his deposition, Dr. Berkland admitted to not having analyzed the scope of the claims-at-issue and appeared unfamiliar with the specification of the '795 Patent, despite it only being four pages long. Ex.1051, 33:4-21, 38:7-22; 119:8-120:23, 160:11-162:16. Having failed to consider the scope of claims 1-24 of the '795 Patent, Dr. Berkland's opinion on the non-obviousness of said claims is not reliable. Consequently, the influence of Dr. Berkland's testimony on the outcome of this proceeding should be minimal and, to the extent that his opinions

Reply (Paper 25), 22

Dr. Berkland Failed to Consider the Scope of the Challenged Claims

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.

Ex. 1001, 5: 34-41 (claim 1)

Q. And do you understand "wherein the syrup formulation" is referencing back to the language in line 34 of column 5 that says "a pharmaceutical syrup formulation"?

(Witness perusing document.)

A. I really haven't conducted that analysis.

Ex. 1051, 33:4-11

Reply (Paper 25), 22

Dr. Berkland Failed to Consider the Scope of the Challenged Claims

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.

Ex. 1001, claim 1

Q. And so what I'm asking you is, is there in agave syrup, in your opinion -- strike that.

Is there a range of viscosities for agave syrup that in your view could not be used in this patent claim?

A. That's a different question; I haven't conducted that analysis.

Ex. 1051, 38:13-22 (objection omitted)

What I'm asking you is, the '795 patent doesn't tell you the type of agave syrup to use, do you agree with me, sir?

A. I didn't look carefully, I didn't conduct that analysis.

Ex. 1051, 120:18-23

Reply (Paper 25), 22

Dr. Berkland Failed to Consider the Scope of the Challenged Claims

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 wherein the acetaminophen is suspended in the syrup.

Ex. 1001, claim 18

Q. Does the patent describe any excipients that would materially affect the basic and novel properties of the claims that are in the '795 patent?
A. I haven't considered that.

Ex. 1051, 160:11-16 (objection omitted)

Q. So as a person of skill in the art reading this patent specification, they would understand that you could use both natural and artificial ingredients in the claims, correct?
A. I haven't formed an opinion there.

Ex. 1051, 161:2-9 (objection omitted)

Reply (Paper 25), 22

Dr. Berkland's Testimony is Unreliable

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.

Ex. 2009, ¶121

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.

Ex. 1031, 1

Reply (Paper 25), 11 fn. 6

The POSITA

The POSITA

KinderFarms' POSITA	Genexa's POSITA
May work alone or as part of a team developing pharmaceutical formulations. He or she has: • A bachelor of science degree in a life sciences discipline relevant to pharmaceutical sciences (e.g., chemistry, biochemistry, biology or pharmacy) and would likely have work experience or other laboratory experience; ***or*** • An advanced degree in a relevant life sciences discipline and less work or laboratory experience; ***or*** • No bachelor degree and several years of experience in the pharmaceutical industry and/or working in a laboratory.	Would have access to one or more team members having experience in pharmaceutical formulation and pharmaceutical regulatory approvals. He or she has: • A bachelor of science degree in a relevant life sciences field (e.g., chemistry, biochemistry, or pharmacy), with at least two years of work or laboratory experience in pharmaceutical formulation; ***or*** • Three to four years of work or laboratory experience in pharmaceutical formulations.

Pet. (Paper 2), 13-14, 13 fns. 6-7; Ex. 1003 (Crowley Decl.), ¶¶90-91, 53 fns. 13 and 14; POR (Paper 20), 10-12; Ex. 2009 (Berkland Decl.), ¶¶19-23

The Prior Art Discloses The Unchallenged Limitations

The Cited Prior Art Teaches "a Stable Pharmaceutical Syrup Formulation for Oral Administration"

FR458

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

Ex. 1004, 3:58-61

WO133

The invention provides an acetaminophen composition in taste-masked form, suitable for oral administration, containing acetaminophen in an aqueous medium. The acetaminophen composition contains acetaminophen in an amount of up to about 10% by weight, preferably from about 2 to about 8% by weight, in an aqueous medium. The aqueous medium contains 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. The additive agent is preferably comprised of sweetening agents which are preferably present in an amount of at least about 25% by weight of the acetaminophen composition.

Ex. 1006, 2:14-25

WO742

In another aspect of the invention, there is provided a pharmaceutical composition, in dosage unit form, for oral administration comprising a safe and effective amount of dextromethorphan and an orally-acceptable pharmaceutical carrier comprising agave nectar, water and ethanol being at a pH of about 3 to about 6.5, wherein the pharmaceutical composition is free of bromide, sodium and polistirex. The composition may include from about 1 mg to about 50 mg dextromethorphan per dose. In some embodiments, the composition is an aqueous-based solution. The composition may be an agave-nectar based liquid.

Ex. 1007, 9:18-25

The '4666 Patent

A stabilized liquid ibuprofen syrup suitable for oral administration comprising: from 50 to 400 mg of ibuprofen per 5 ml of syrup; said ibuprofen 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, abstract

See Pet. (Paper 2), 29-28, 38-39; 56, 61-62; Ex. 1003 (Crowley Decl.), ¶¶106-108, 138-143, 201-203, 233-237, App. D, 1-2, 15-16, 49-51, 62-64; Reply (Paper 25), 12 fn. 8

Genexa Does Not Dispute that "a Stable Pharmaceutical Syrup Formulation for Oral Administration" is Disclosed

142. FR458, the '4666 Patent and WO133 all make it clear that the formulations they disclose are ultimately intended to be orally administered to patients. Ex. 1004, at p. 1, lns. 4-5 ["This invention relates to novel liquid pharmaceutical formulations for oral administration."], at p. 3, lns. 58-62, at p. 12, lns. 4-6 (claim 1); Ex. 1006, at p. 2, lns. 14-25 ["The invention provides an acetaminophen composition in a taste-masked form, suitable for oral administration, containing acetaminophen in an aqueous medium…"], p. 1, ln. 11 – p. 2, ln. 12; Ex. 1005, at 2:15-21 ["The stabilized liquid ibuprofen formulations of this invention include both sucrose sweetened and sugar free formulations suitable for administration to diabetics and other patients whose sugar intake should be restricted...."], at abstract, at 1:6-15, at 6:19-25 (claim 1). Therefore, a person of ordinary skill in the art would have understood that the formulations disclosed in FR458, WO133 and the '4666 Patent are, necessarily, stable formulations because they are all meant to be administered to patients.

Ex. 1003, ¶142

See POR (Paper 20) and Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches "a Diluent" that is Water

FR458

Example 1

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

Ex. 1004, 8

The '4666 Patent

EXAMPLE I

A 1,000 gallon batch of aqueous syrup for oral use, containing 200 mg of ibuprofen per 5 ml, one teaspoon, dose is prepared from the following:

Ibuprofen (micronized)	151 kg
Sorbitol	2322 kg
Glycerol	710 kg
Ethanol (95%)	800 kg
Veegum	10 kg
PVP	5 kg
Sodium metabisulfite	8 kg
Sodium hydroxide	21 kg
Carmine solution*	61 kg
Wild cherry flavor (Cosomo #37)	7 kg
Sodium saccharin	20 kg
Butyl paraben	0.65 kg
Propyl paraben	0.36 kg
Deionized water, q.s.	1000 gal

Ex. 1005, 4

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

See Pet. (Paper 2) , 30, 39, 42-43, 57, 61-62, 64-65; Ex. 1003 (Crowley Decl.), ¶¶,116-118, 155-156, 159-160, 211-214, 247-248, 251-252, App. D, 6-7, 23-24, 30-32, 42-44, 54-55, 70-71, 76-78

Genexa Does Not Dispute that "a Diluent" that is Water is Disclosed

. FR458 teaches that water is added to the formulation as required to bring it to the desired total amount. Ex. 1004, Example 1 (purified water is added "up to" 100 mL), 8, lns. 199- 204 (explaining that "the water is topped up to 100 ml and everything is mixed together."). Similarly, the '4666 Patent teaches adding water to the formulation in Example 1 to achieved the final desired volume of 1000 gal. Ex. 1005 at col. 4, ll. 40-56 (Example 1). A person of ordinary skill in the art would understand that amount of water serves to bring the formulation to the desired volume and can be modified within reason without altering the effectiveness of the formulation. Ex. 1003 at ¶ 155.

Pet. (Paper 2), 42

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches "Acetaminophen Suspended in the Syrup"

FR458

The xanthan gum and the agar-agar are mixed with the glycerin to obtain Solution A. The paracetamol is suspended 225 [sic] in the syrup to obtain Solution B. Solution A is added to Solution B and mixed well. The water is topped up to 100 ml and everything is mixed together. The preparation is placed in vials.

Ex. 1004, 8:199-204

WO133

The acetaminophen composition of the present invention is characterized by having a palatable taste and with only a slight gritty feel. The composition is a liquid formulation in which the acetaminophen is suspended, and slightly dissolved, in an aqueous medium containing a suspension agent for dispersing the acetaminophen and an additive agent that decreases the solubility of the acetaminophen in the aqueous solution. The additive agent is preferably a sweetening agent.

Ex. 1006, 3:8-15

WO742

The compositions of the present invention are intended for oral administration. Examples of such compositions include preferred liquid compositions, especially aqueous-based liquid compositions, such as syrups, elixirs, suspensions, sprays, and drops.

Ex. 1007, 13:7-10

See Pet. (Paper 2), 20-24, 25-26, 32-33, 39, 41-42, 47, 58-59; Ex. 1003 (Crowley Decl.), ¶¶65, 77, 80, 122-123, 126, 138, 175, 100, fn. 20, ¶¶ 219-220, 233, App. D, 8-10, 25-27, 44-47, 56-58, 72, 74,

Genexa Does Not Dispute that "Acetaminophen Suspended in the Syrup" is Disclosed

FR458, the '4666 patent, and WO133 each teach that the API can be suspended in an oral formulation. Ex. 1004, at 2, lns. 39-55, at 3, lns. 58-68; 7, lns. 187-198, 8, lns. 199-204 (including Example 1), 10, ln. 221- 11, ln. 245 (including Example 4); Ex. 1005 at col. 2, lns. 41-48, col. 3, 50-53; Ex. 1006; at abstract; at 2, ln. 13-3, ln. 3, 3, lns. 7-18 ("The composition is a liquid formulation in which acetaminophen is suspended. . . ."), 4, lns. 16-28, 8, lns. 17-24, 13, ln. 24 – 14, ln. 6. A person of ordinary skill in the art would understand that each of these references teaches this limitation. Ex. 1003 at ¶¶ 122-123.

Pet. (Paper 2), 32-33

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches "the Syrup is Palatable"

FR458

Solid dosage forms are not suitable for children or for the elderly. This is why they are formulated in liquid dosage forms, either in a clear syrup or a suspension. Furthermore, some drugs such as cough suppressants are preferably prepared in liquid dosage forms. Some drugs are formulated in suspension either due to insufficient solubility or to mask an unpleasant taste.

Ex. 1004, 2:39-45

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

WO133

The present invention relates to acetaminophen compositions in which the acetaminophen is presented in taste-masked form. More particularly, the present invention relates

Ex. 1006, 1:4-6

The '4666 Patent

The stabilized liquid ibuprofen formulations of this invention include both sucrose sweetened and sugar free formulations suitable for administration to diabetics and other patients whose sugar intake should be restricted. Because of the bitter and unpleasant flavor of ibuprofen, it is desirable to have a product of high sweetness.

Ex. 1005, 2:15-21

See Pet. (Paper 2), 16, 33, 38-39, 47-51, 58-59, 61, 63, 68-69; Ex. 1003 (Crowley Decl.), ¶¶73, 76, 95, 124-129, 148-150, 173, 177-178, 221-224, 240-242, App. D, 10-12, 35-37, 58-59 .

Genexa Does Not Dispute that "the Syrup is Palatable" is Disclosed

128. A POSITA would have understood that the oral formulations disclosed in FR458, the '4666 Patent, and WO133 that contain the APIs acetaminophen and/or ibuprofen, which both have an unpleasant taste when dissolved in water, would have been rendered palatable by virtue of suspending the API(s) in a liquid composition with a high degree of sweetness and/or added flavoring.

Ex. 1003 (Crowley Decl.), ¶128

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches an "Acidic Preservative" That Comprises "Citric Acid"

FR458

Example 1

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

Ex. 1004, 8

WO133

The pH of the acetaminophen composition is held below about 6, and most preferably between about 3.5 and 5. 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. Any appropriate ingestible acid may be used to modify the pH of the acetaminophen composition, including hydrochloric, citric, and acetic acid.

Ex. 1006, 7:20-26

See Pet. (Paper 2), 40, 44, 47, 48, 61, 63, 66; Ex. 1003 (Crowley Decl.), ¶¶63, 65, 144-147, 165-166, 175-176, 238, 256-257, App. D., 20-21, 32-33, 39-40, 68, 78

Genexa Does Not Dispute that an "Acidic Preservative" That Comprise Citric Acid is Disclosed

In the examples provided FR458, sodium citrate and anhydrous citric acid are both included in each of the formulations described in the four Examples. Ex. 1004, at pp. 8-10, examples 1-4. A person of ordinary skill in the art would have understood that excipients are multifunctional and that pH regulating agents like citric acid and sodium citrate can also act as weak acidic preservatives in a formulation – by lowering the pH of drug formulations, they can help to slow microbial growth and help to limit other undesirable changes in the formulation (e.g., physical, chemical). Moreover, in their buffering capacity, they act to create an ideal environment for the anti-microbial activity of other acidic preservatives, like sorbic acid.

146. WO133 also discloses formulations that can contain preservatives, such as the acid preservative sorbic acid, and pH regulating agents, such as citric acid. Ex.

Ex. 1003 (Crowley Decl.), ¶¶145-146

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches "a Flavoring Agent" That is a "Bitter-Taste-Blocking Ingredient"

WO133

The additive agent is preferably comprised of a sweetening agent or mixtures of sweetening agents so that not only is the bitter taste of the acetaminophen in solution limited, but it is replaced by the pleasant tasting sweetener. Other agents, besides sweetening agents, can also be used to limit the solubility of the acetaminophen. These agents

Ex. 1006, 5:21-26

The '4666 Patent

The stabilized liquid ibuprofen formulations of this invention include both sucrose sweetened and sugar free formulations suitable for administration to diabetics and other patients whose sugar intake should be restricted. Because of the bitter and unpleasant flavor of ibuprofen, it is desirable to have a product of high sweetness.

Ex. 1005, 2:15-21

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

See Pet. (Paper 2), 25, 40-41, 46, 63, 67-68; Ex. 1003 (Crowley Decl.), ¶¶148-150, 173-175, 240-242, 264-265, App. D, 21-23, 34-35, 40-42, 68-70, 79-81

Genexa Does Not Dispute that "a Flavoring Agent" That is a "Bitter-Taste-Blocking Ingredient" is Disclosed

A person of ordinary skill in the art would understand that acetaminophen and ibuprofen are bitter tasting medicines. Such a person would also understand that FR458, WO133 and the '4666 Patent teach oral formulations that contain these medicines and flavoring agents, which are included to mask the unpleasant (i.e., bitter) taste of the medicines.

Ex. 1003 (Crowley Decl.), ¶173

See POR (Paper 20), generally, Sur-Reply (Paper 29), generally

The Cited Prior Art Teaches "Wherein the Agave Syrup is Less Than [98% or 95%] of the Formulation by Weight"

FR458

Example 1

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

Ex. 1004, 8

WO742

EXAMPLE IX. Liquid Cough Composition Ingredients Amount/15 ml Dose:

Acetaminophen	160.0
Dextromethorphan Hydrochloride monohydrate	9.0 mg
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
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, 23

See Pet. (Paper 2), 43-44, 53-54, 65; Ex. 1003 (Crowley Decl.), ¶¶157-158, 249-250, App. D, 29-30, 48-48, 75-76

Genexa Does Not Dispute that "Wherein the Agave Syrup is Less Than [98% or 95%] of the Formulation by Weight" is Disclosed

157. Examples 1-4 of FR458 disclose pharmaceutical syrup formulations that clearly contain less than 98% or 95% agave syrup by weight. For example, without even accounting for the weight of the water that will be used to bring the formulation to the final desired volume of 100 mL, the amount of agave syrup included in the formulation in Example 1 only corresponds to 83% of the total weight of the formulation ingredients. *See, e.g.*, Ex. 1004, at p. 8, example 1. Moreover, a person of ordinary skill in the art would have been aware that medicinal formulations could contain less than 98% agave syrup by weight. *See, e.g.*, Ex.1008.

249. WO742 discloses formulations that contain amounts of agave nectar that meet these limitations. For example, a person of ordinary skill in the art would have understood that the amount of agave nectar present in the formulation of Example V of WO742 could not possibly exceed 95% or 98% of the total weight of the formulation, based on the weight of the other components in the formulation.

Ex. 1003 (Crowley Decl.), ¶¶157, 249

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally

The Prior Art Teaches "Wherein the Formulation is Orally Administered for Veterinary and Human Use"

WO742

In another aspect of the invention, there is provided a method of treating or preventing cough in humans by orally administering to the human a safe and effective amount of a composition of the present invention.

Ex. 1007, 9:26-28

WO133

Acetaminophen is commonly taken as a tablet by the vast portion of the population. However, the tablet form is hard to administer in treating the elderly and the young. Therefore, liquid formulations of acetaminophen are commonly administered for these patients. However, in liquid form such

Ex. 1006, 1:13-17

The '4666 Patent

This invention relates to medicinal orally administrable stabilized liquid analgesic compositions, and more specifically relates to stabilized liquid analgesic compositions having ibuprofen (p-isobutylhydratropic acid) as their active ingredient. These compositions, which have the form of moderately viscous syrups, are useful for the treatment of pain, inflammatory conditions and other conditions including adult respiratory distress syndrome.

Ex. 1005, 1:6-15

See Pet. (Paper), 45, 45 fn. 23, 67; Ex. 1003 (Crowley Decl.), ¶¶170-172, 261-263, App. D, 33-34, 79

Genexa Does Not Dispute that "Wherein the Formulation is Orally Administered for Veterinary and Human Use" is Disclosed

170. Claim 16 adds a limitation that the formulation be orally administered for veterinary and human use. It is not clear whether this claim is attempting to claim a formulation or a method of use of this formulation. Either way, the specification of the '795 Patent does not describe any of the formulations as "orally administered for veterinary and human use" or provide any guidance as to what this claim limitation signifies. A person of ordinary skill in the art would have understood that the pharmaceutical formulations for oral administration disclosed in FR458, the '4666 Patent and WO133 would likely be administered to humans and/or other mammals.

Ex. 1003, ¶170

See POR (Paper 20), generally; Sur-Reply (Paper 29), generally