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EXAMINER

CAMPELL, BRUCE R

ART UNIT

3991

MAIL DATE

06/05/2018

DELIVERY MODE

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.
NUVO RESEARCH AG, Respondent v. Patent of NEURALTUS PHARMACEUTICALS, INC.,

Appeal 2018-004289
Reexamination Control 95/002,106
Patent 8,067,035 B2
Technology Center 3900


LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal by the Patent Owner from the Patent Examiner’s rejection of claims 1–18 in the above-identified inter partes reexamination of United States Patent 8,067,035 B2. The Board’s jurisdiction for this appeal is under 35 U.S.C. §§ 6(b), 134, and 315 (pre-AIA). The Examiner is affirmed.
I. STATEMENT OF THE CASE


The Examiner made a determination that claims 1–18 are unpatentable under 35 U.S.C. § 103. Patent Owner appeals from the grounds of rejection set forth by the Examiner. Appeal Br. 3.

Requester filed a Respondent Brief, but the brief was stricken from the record. See Decision on Petition (entered Jan. 27, 2017).

Patent Owner provided two declarations under 37 C.F.R. § 1.132 during the prosecution of the ’035 patent that have been considered in this appeal. These declarations are:

Declaration by Michael McGrath, M.D., Ph.D., dated May 27, 2011, discussing hematologic problems associated with WF10 administration (“1st McGrath Decl.”).

Declaration by Michael McGrath, M.D., Ph.D., dated May 27, 2011, discussing unexpected pH stability associated with claimed pharmaceutical (“2nd McGrath Decl.”).

Requester provided three declarations under 37 C.F.R. § 1.132 during the proceeding before the Examiner that have been considered in this appeal. These declarations are:
Declaration by Rainer Martin, Ph.D., dated January 29, 2013, discussing the McGrath pH experiments described in the 2nd McGrath Declaration (“1st Martin Decl.”).

Declaration by Rainer Martin, Ph.D., dated February 4, 2013, discussing the cited prior art publications (“2nd Martin Decl.”).

Declaration by Henrich Guntermann, M.D., dated February 5, 2013, discussing the unexpected results relating to hemoglobin side effects described in the 1st McGrath Declaration (“Guntermann Decl.”)

Patent Owner contends that the Examiner erred by allowing entry and considering the Martin and Guntermann declarations. Appeal Br. 3–6.

Our review for the purpose of an appeal is of a rejection of a claim. Pre-AIA 35 U.S.C. § 134(b). We do not have jurisdiction over an Examiner’s action in deciding whether or not to admit a declaration. A dispute with an Examiner’s action in entering a declaration may be addressed by a timely filed petition. See, e.g., 37 C.F.R. § 1.181(a)(1). It is not subject to review in an appeal under 35 U.S.C. § 134(b). Thus, we have not considered the propriety of the Examiner’s action in admitting the declarations. Because the Examiner entered the declarations into the record, we have taken them under consideration in this Decision on Appeal.

CLAIMS

Claims 1–18 stand rejected by the Examiner. There are two independent claims on appeal, claims 1 and 2. Claim 1 is representative and reads as follows:
1. A pharmaceutical composition comprising: (a) an aqueous solution comprising sodium chlorite, wherein the weight ratio of chlorite: chlorate is greater than 100: 1.5, and the concentration of chlorite is at least 60 mM; (b) a phosphate buffer; and (c) a pharmaceutically acceptable excipient; wherein the composition is a sterile intravenous solution having a pH between about 7 and about 9.5.

Claim 2 recites the same limitations, but is directed to a unit dosage.

REJECTIONS

The claims stand rejected by the Examiner as follows:

1. Claims 1 and 6–18 under pre-AIA U.S.C. § 103(a) as obvious in view of Kühne I ’922 and Mullerat, as evidenced by Kühne II ’285,

1 To the extent that the Examiner used the term “or” in reciting the list of cited prior art publications, we have considered all the publications to define the scope and content of the prior art (Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966)) and stated the rejection in this way.


Steffen,5 Shahangian,6 Inorganic Ventures,7 Danner,8 Tissot,9 and McGrath II.10 RAN 4.


3. Claims 1–18 under 35 U.S.C. § 103(a) under pre-AIA U.S.C. § 103(a) as obvious in view of McGrath I12 and Mullerat, as evidenced by Shahangian, Inorganic Ventures, Tissot, the Immunokine product insert, and McGrath II.

CLAIM INTERPRETATION

Independent claims 1 and 2 are directed to pharmaceutical compositions that comprise sodium chlorite “wherein the weight ratio of

7 Inorganic Ventures, Certificate of Analysis for I-CAL ION CHROMATOGRAPHY SOLUTION of chlorite in water.
11 Data and Instructions for the Use of IMMUNOKINE WF10 (TCDO) I.v. Solution for Intravenous Infusion.
chlorite: chlorate is greater than 100: 1.5.” The claims recite that “the composition is a sterile intravenous solution having a pH between about 7 and about 9.5.” While the composition is intended to be used intravenously, we could not find, and have not been directed to, disclosure in the ’035 patent which identifies characteristics of an intravenous solution that would distinguish it from other compositions for pharmaceutical use.

The claimed weight ratio of chlorite to chlorate of “greater than 100: 1.5” includes compositions where the ratio is so large that only a small amount of chlorate is present, e.g., where chlorate is at a 0.5 weight ratio to 100 parts chlorite (claim 13) or less.

FINDINGS OF FACT (“FF”)

’035 Patent

FF1.

Chlorite has also been used to treat various diseases or conditions. For example, chlorite has been used to treat infections and to cause regeneration of bone marrow. See, for example, U.S. Pat. No. 4,725,437 and U.S. Pat. No. 4,851,222. Chlorite has also been used to treat HIV, recurrent prostate cancer, cystitis, and chronic active hepatitis C disease. See, for example, McGrath et al., Development of WF10, a novel macrophage-regulating agent, *Curr Opin Investig Drugs*, 3(3):365–73 (March 2002). [Cited as “McGrath II” in this reexamination] These diseases or conditions have generally been treated with intravenous injection of WF10, a commercially available formulation of chlorite. The approximately 12.3 pH of this formulation may be problematic for some forms of administration to physiological systems.

’035 patent, col. 1, ll. 21–34 (“Background”).
The non-chlorite elements of TCDO [WF10 as described in Kühne II ’285] in these various forms, for example the chlorate ions, may cause undesirable effects when administered to physiological systems. For example, ingestion of sodium chlorate causes irritation to the gastrointestinal tract, and may result in nausea, vomiting and diarrhea. Mallinckrodt Baker Inc. MSDS S3314, Aug. 10, 2004. Other symptoms include abdominal pain, hemolysis, methemoglobinemia, cyanosis, anuria, coma, and convulsions. Id. Further, exposure to sodium chlorate may cause liver and kidney damage, and repeated ingestion of small amounts may cause loss of appetite and weight loss. Id. ’035 patent, col. 1, ll. 57–67 (“Background”).

Kühne II ’285

This invention relates to stabilized activated oxygen which is incorporated in a matrix of chlorite ions, and pharmaceutical compositions containing this stabilized activated oxygen.

Kühne II ’285, col. 1, ll. 7–10.

While here, the maximum anticipated yield of ClO₂⁻ [chlorite] has not yet been completely attained, the ClO₃⁻ [chlorate] content is still very small. Increasing OCl⁻ [hypochlorite] concentrations of course do yield more ClO₂, this is accomplished at the expense of increased chlorate formation.

Kühne II ’285, col. 2, ll. 63–68.

The presence of undesired chlorate is evidenced by a band at 937 cm⁻¹.
An excessively high hydrogen ion or hypochlorite concentration would favor the formation of chlorate (oxidation of ClO₂⁻ [chlorite] to ClO₃⁻ [chlorate]) due to the increased oxidizing effect.

FF7.

The activated oxygen stabilized according to the invention, which is contained in a matrix of chlorite ions, can be used in various fields, for example, in medicine and in veterinary medicine, in cosmetics, for the sterilization of food and drinking water, and as feed additives.

Example I describes making a chlorite solution, where the “solution obtained had a pH value of between 13.5 and 13.8.” Kühne II ’285, col. 4, ll. 10–11.

Example III describe a pharmaceutical preparation:

A medicinal solution was made from the product in Example 1 by diluting it with distilled water in a ratio of 1:50; that medication had a pH value of 11.45–11.6 and was physiologically tolerated.
Mullerat

FF10.

Mullerat describes orally administering a pH-buffered composition comprising chlorite and chlorate ions to food animals. Mullerat, col. 19–20 (claim 1).

FF11.

A preferred molar ratio of chlorite ion source to chlorate ion source that is added to the water-containing solvent is in the range from 2:1 to 500:1, that of chlorite ions to chloride ions is in the range from 0.1:1 to 50:1 and that of chloride ions to chlorate ions is in the range from 0.1:1 to 500:1.

A still more preferred embodiment of the invention employs compositions wherein the molar ratio of chlorite ion to chlorate ion is in the range from 2:1 to 16:1; the molar ratio of chlorite ion to chloride ion is in the range from 0.8:1 to 5:1; and the molar ratio of chloride ion to chlorate ion is in the range from 1.5:1 to 16:1.

Mullerat, col. 4, ll. 11–21.

FF12.

The stability of the compositions can be improved by adding a pH-adjusting material to adjust the pH of the resulting mixture to a final range of 7.5 to 13. It has been found that if the pH is adjusted to about 13, the compositions are very stable and will retain their biocidal properties over long periods of storage. The concentration of the buffer can range from 0.001 M up to the saturation level of the solution. The preferred buffering ingredients contain phosphate salts.

Mullerat, col. 4, ll. 28–35.
Chlorate poisoning is associated with methaemoglobinaemia.

In the case described by Steffen and Seitz (1981), a very high dose of sodium chlorate (150-200 g) was ingested. Methaemoglobinaemia was followed by haemolysis, disseminated intravascular coagulation and renal failure.

Tissot describes injecting WF10 into the pleural cavity of rats to test its effect on inflammation. Tissot teaches that “WF 10 was adjusted to physiological pH (7.4) immediately prior to use.” Id. at 369 (“Reagents”). Tissot also teaches diluting with phosphate-buffered saline for in vitro experiments with cells. Id. (column 2).

IMMUNOKINE® (WF10 Solution) MUST BE DILUTED with a suitable dilutant prior to intravenous infusion. IMMUNOKINE® MUST BE DILUTED in either physiological saline solution, Ringer solution or glucose 5% solution to prepare 250 to 500 cc ready to use solution.
Danner

FF16.

Danner describes compositions and methods for facilitating the healing of dermal disorders in human skin, including wound healing. Danner, col. 5, ll. 26–31. Danner describes a composition for therapeutic and prophylactic treatment of human skin which comprises an aqueous solution of a metal chlorite, such as sodium chlorite or potassium chlorite, in a concentration of from about 0.002% (20 ppm) to about 0.5% (5,000 ppm). The pH of the solution should be in the range of about 6.0 to about 10.0 and any stable buffer useful in the stated pH range may be used.

Danner, col. 6, ll. 16–23.

FF17.

Carbonate, borate, phosphate or combinations thereof may be used as a buffer for the solution.

Danner, col. 6, ll. 32–33.

FF18.

In alternative embodiments, the compositions of the present invention include aqueous mixtures of metal chlorites, such as sodium or potassium chlorite, and metal chlorates, such as sodium or potassium chlorate.

Danner, col. 6, ll. 45–48.

FF19.

The ratio of chlorite to chlorate in the solution can be from about 100:0% up to about 60:40%, with the ideal composition for each application dependent upon the usage and nature of treatment being administered.

Danner, col. 6, ll. 54–57.
WF10 is a sterile, pyrogen-free, aqueous 10% (w/v) solution of OXO-K993 with no additional inactive ingredients and is intended for intravenous infusion. OXO-K993 has been analytically characterized as an aqueous solution containing chlorite ion (4.25%) as the active principle, and the inactive ingredients chloride (1.9%), chlorate (1.5%) and sulfate (0.7%) ions, with sodium as the cation.

Inorganic Ventures

Inorganic Ventures describes a chlorite solution comprising 12 ± μg/ml of ClO₃⁻ (chlorate), 6 ± 1 μg/ml of Cl⁻ (chloride), and 998 ± 3 μg/ml of chlorite.

REJECTION 1

Ratio limitation
The claims require a weight ratio of chlorite: chlorate which is greater than 100: 1.5.

Rejection
The Examiner found that Kühne I ’922 discloses a chlorite solution for the treatment of HIV. RAN 4. The composition and pH of the chlorite solution is not described by Kühne I ’922, but the Examiner found that Kühne I ’922 teaches that the same solution – WF10 – is described in Kühne II ’285. RAN 4 (“The chlorite matrix, designated as WF10 in the following experiments, was produced in accordance with Example 1 of U.S. Pat. No.
The Examiner acknowledged that neither Kühne I ’922 nor Kühne II ’285 describes the ratio of chlorite to chlorate recited in the claims. *Id.* at 4–5. However, the Examiner found such ratio is encompassed by the broad disclosure in Mullerat. *Id.* at 5. The Examiner also cited Inorganic Ventures and Shahangian as evidence of the commercial availability of chlorite solutions meeting the recited chlorite to chlorate ratio. *Id.* The Examiner determined it would have been obvious to one of ordinary skill in the art to replace the WF10 solution in Kühne I ’922 and Kühne II ’285 with a solution containing a minimal amount of chlorate because chlorate was known to be toxic to humans. *Id.* at 6. The Examiner cited Steffen as evidence of the toxicity of chlorate. *Id.* The Examiner also cited the teaching in Kühne II ’285 that the presence of chlorate in WF10 is undesirable. *Id.* at 16.

*Patent Owner’s arguments*

Patent Owner contends that there must be a reason for a person of ordinary skill in the art to have replaced “a high-chlorate solution of Kühne I [’922] with a low-chlorate composition as claimed.” *Appeal Br.* 7. Patent Owner acknowledged “Mullerat discloses a preferred chlorite:chlorate molar ratio for the composition of Mullerat which is between 2: 1 and 500: 1, which would overlap slightly with the claimed range.” *Id.* However, Patent Owner contends that Mullerat “teaches away from using low-chlorite compositions because most embodiments of Mullerat, including those characterized as the best embodiments, along with the working examples,
use much higher chlorate levels than those recited in the independent
claims.” *Id.* Patent Owner also contends the Mullerat teaches chlorate is
beneficial. *Id.* at 7–8. Patent Owner further contends that Steffen doesn’t
supply the “missing motivation” to have used a low-chlorite solution
because Steffen’s conclusions are based on high concentrations of chlorate,
orders of magnitude higher than those which are claimed. *Id.* at 8–9. Patent
Owner states:

Guided by the teachings of Steffen, a skilled person would
consider the chlorate level in the WF10 composition of Kühne I
[’922] or in the composition of Mullerat to be *de minimis* and
very unlikely to cause chlorate poisoning, and would see no
further need to lower it.

Appeal Br. 9.

Patent Owner also contends that Mullerat is non-analogous prior art
and not in the same field of the invention because it relates to oral
compositions to be added to animal feed. Appeal Br. 13–14. Patent Owner
contends:

. . . a skilled person seeking to prepare a sterile pharmaceutical
formulation for intravenous administration, which can be
administered to human subjects, would be very hesitant to rely
on the teaching of a reference disclosed as applicable only to
feed animals and only by oral administration.

Appeal Br. 14.

Discussion

The Examiner’s reason to have minimized the chlorate in WF10
taught in Kühne I ’922 and Kühne II ’285 is because of the toxicity of the
chlorate ion and its undesirability. RAN 6, 16. The Examiner’s reasoning is supported by a preponderance of the evidence.

First, while it is unchallenged by the Examiner that Steffen’s concentrations of chlorate are higher than the amounts in WF10 that would be administered by Kühne I ’922, the Examiner’s response is scientifically logical and factually supported: Chlorate is not an active ingredient of WF10 (FF20) and a skilled artisan would not “include a substance known to cause hypoxia, hemolysis, coagulation disturbances and renal failure in a composition intended for intravenous administration, absent some expected benefit.” RAN 16.

Second, as found by the Examiner, Kühne II ’285 teaches that chlorate is undesirable. FF4, FF5. Accordingly, one of ordinary skill in the art would have sought to minimize it, making it reasonable to have utilized the low-chlorate commercial compositions (Shahangian, Inorganic Ventures) identified by the Examiner. RAN 5. There is no requirement in the claim that quantities of the chlorite solution be available or cost-effective for “large-scale commercial use” as argued by Patent Owner. Appeal Br. 10. Patent Owner contends “[i]t is not clear from the cited references that such amounts could be obtained on a practical scale and at a reasonable cost,” but Patent Owner has provided no objective evidence or scientific reasoning to support this contention. Id. at 10–11.

Patent Owner attempts to diminish the disclosure in Kühne II ’285 that chlorate is “undesired” (FF5) by arguing that the skilled worker would have recognized the levels of chlorate present in WF10 taught by Kühne II
’285 are acceptable and there would be no reason to lower them. Appeal Br. 10.

However, Patent Owner cited the Veerasarn publication as teaching that “74% of patients treated with WF10 exhibited hemoglobinemia, compared to 35% of control patients” and that “Veerasarn provide clear evidence that WF10 induces hemoglobinemia as a side effect of treatment.” Appeal Br. 21. While Veerasarn does not teach the chlorate ion is responsible for the deleterious effect, in view of the teachings in Steffen (FF13) and Kühne II ’285 (FF4, FF5) about its toxicity and undesirability, one of ordinary skill in the art would have reason to minimize chlorate’s presence.

Third, Patent Owner’s challenge to Steffen based on the pertinence of its teaching of toxicity because its chlorate concentrations are said to be “many orders of magnitude higher than those of the claimed compositions” (Appeal Br. 8–9) is inconsistent with Patent Owner’s own disclosure in the ’035 patent. The ’035 Patent in its “Background” section teaches that “non-chlorite elements of TCDO [as described in Kühne II ’285; also known as WF10] in these various forms, for example the chlorate ions, may cause undesirable effects when administered to physiological systems”, such as GI irritation and that “repeated ingestion of small amounts may cause loss of appetite and weight loss.” FF2. Thus, Patent Owner acknowledged in its

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own patent that it was known that even “small amounts” of chlorate may have deleterious effects.

Fourth, Danner describes a solution which ranges from no chlorate to higher amounts of it, “dependent upon the usage and nature of treatment being administered.” FF19. Danner’s solution is for application to wounds, and, therefore, is in contact with a cellular environment, making it pertinent to the medical application of Kühne I ’922, which also involves administration to a cellular environment (intravenous). Danner’s disclosure indicates the routineness of choosing a desired level of chlorite to chlorate, depending on the composition’s specific application.

Patent Owner states that the teaching in McGrath II that chlorate is an inactive ingredient would have been a disincentive to remove it from the chlorite solution. Appeal Br. 10. We do not agree. Known undesirable effects incentivize the ordinary artisan to remove inactive, unnecessary ingredients that cause those effects. McGrath II teaches that chlorite is the “active principle” in regulating macrophage function, while the chlorate ion does not possess such activity and, thus, is “inactive” with respect to this activity. McGrath II (first page) (FF20). McGrath II was not addressing whether the chlorate ion was deleterious when administered, which Patent Owner acknowledges it is in its own ’035 patent. FF2.

Patent Owner also attempts to distinguish the prior art by arguing that the cited Shahangian or Inorganic Ventures publications use the chlorite solutions disclosed therein for a different purpose. Appeal Br. 10–11.

This argument is not persuasive. The Examiner relied on these publications to demonstrate that chlorite compositions meeting the claimed
ratio were known and available in the prior art, and, thus, once motivated to use a low chlorate composition due to the undesirable effects of chlorate, the prior art enabled the skilled worker to obtain low chlorate composition, including those that have chlorite to chlorate ratios within the range recited in the claims. Patent Owner did not distinguish the ratio of chlorite to chlorate in its claims from the ratio of the solution described in the publications cited for this purpose, such as Inorganic Ventures.

With regard to the arguments that Mullerat is non-analogous prior art, we agree that the Mullerat’s chlorite solution is being used for a different purpose than Kühne I ’922 – as oral animal feed additive versus as an intravenous medical treatment. However, Kühne II ’985 describes the field broadly, stating that the chlorite solution can be used in medicine, veterinary medicine, and as feed additives. FF7. Thus, Mullerat is still pertinent to Kühne II ’985. Nonetheless, we have relied upon the ratio disclosed in Mullerat for chlorite to chlorate (FF11) only to the extent that chlorite solutions within the scope of the claim could be made and were routinely used, as also evidenced by Inorganic Ventures (FF21).

We find that there was a fact-based reason at the time of the invention to have utilized chlorite solutions with as low as possible chlorate to reduce the likelihood of adverse events when administered intravenously as taught by Kühne I ’922 and Immunokine (FF2, FF13), and because chlorate is undesirable (FF4, FF5). Moreover, Patent Owner has not distinguished its chlorite solution from the chlorite solution of Inorganic Ventures, nor from Danner’s which is also for pharmaceutical use, specifically for application to wounds on human skin (FF16).
Dependent claim 12

Dependent claim 12 is directed to the “composition of claim 1, wherein the concentration of chlorite is between about 1 M and about 1.5 M.”

While we recognize that the Examiner relied upon Mullerat as teaching a composition having 1M chlorite (RAN 6), it was known in the art to dilute a composition comprising chlorite prior to intravenous administration as taught by Immunokine (FF9, FF15). In other words, while a lower molarity might be desirable for administration purposes, it was known to store a solution at a higher molarity prior to diluting it in an appropriate diluent when preparing the chlorite solution for intravenous administration. Consequently, absent evidence to the contrary, we discern no criticality to the chlorite concentration. Thus, we do not find Patent Owner’s argument based on Mullerat to be persuasive (Appeal Br. 15–16) since the significance of a higher chlorite concentration for storage or other purposes has not been established.

Dependent claim 13

Dependent claim 13 is directed to the “composition of claim 1, wherein the weight ratio of chlorite:chlorate is greater than 100:0.5.”

Patent Owner contends that this claim is separately patentable because “Mullerat further teaches away from selecting a low level of chlorate because Mullerat teaches that chlorate is a beneficial additive.” Appeal Br. 16.
We have already discussed that the preponderance of the evidence supports the determination that it would have been obvious to minimize the chlorate concentration because it described as undesirable (FF4, FF5) and is admitted to have deleterious effects (FF2, FF13). Patent Owner has not demonstrated the criticality of the claimed ratio.

[The] law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims…in such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.

*In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Dependent claims 14–16

Dependent claims 14 and 15 are directed to particular weight ratios of chlorite to sulfate, i.e., “greater than 100: 16.4” and “greater than 100: 1.6,” respectively. Claim 16 is to no more than 1 part sulfate in 1000 per weight of solvent. Thus, claims 14–16 read on as little as *de minimus* amounts.

The Examiner relied upon Shahangian and Inorganic Ventures for their teaching of chlorite solutions within the scope of claim 1. RAN 5, 9, 15 (“The rejection states that it would have been obvious to modify the chlorite containing solution of Kühne I by replacing WF10 with a solution of sodium chlorite containing a minimal amount of chlorate, adjusted to physiological pH with phosphate buffer.”). There is no evidence that these
solutions comprise sulfate. The Examiner also found that Mullerat describes a chlorite solution lacking sulfate. RAN 6.

Patent Owner contends that all Mullerat’s examples comprise sulfate. Appeal Br. 16.

However, Mullerat does not require sulfate to be present in any particular amount or the presence of sulfate at all. Rather, Mullerat states that “sulfates can also be utilized to retard the formation of chlorine dioxide” (Mullerat, col. 4, ll. 38–44), indicating that sulfates may be included when it is desired to control the level of chlorine dioxide. While the working examples of Mullerat may all contain sulfate, there is no teaching that the amount present is the only workable amount or that the sulfate is even necessary. To the extent this disclosure could be interpreted as a preference for sulfate, a non-preferred embodiment, i.e., chlorite without sulfate, is not any less a prior art disclosure than a preferred embodiment, but rather simply reflects the inventor’s choice of one suitable alternative for another.

Moreover, Patent Owner has distinguished Mullerat’s compositions as being feed additives, not pharmaceutical preparations for intravenous use. Appeal Br. 13–14. Consequently, the need for a retardant in the quantities described by Mullerat might be different when the chlorite is used as an additive to water for oral ingestion by animal as taught by Mullerat (FF10), rather than when used as a pharmaceutical composition for intravenous use as taught by Kühne I ‘922 or Immunokine. Patent Owner did not direct us to evidence that sulfate is must be present in any particular amount or is necessary in a composition intended for intravenous administration.
Nonetheless, even if sulfate is present as a retardant in an intravenous composition, it would have been obvious to determine an effective amount when used in a pharmaceutical composition because it is a result-effective parameter that would require only routine optimization to determine such effective amount. We have not been directed to evidence to the contrary.

In addition to this, McGrath II, which discloses a composition for intravenous solution, expressly teaches that the sulfate present in WF10 is an “inactive ingredient[ ].” Accordingly, one of ordinary skill in the art would have regarded the sulfate as dispensable and non-critical and that de minimus amounts of sulfate are suitable for use.

Claim 17

Dependent 17 is directed to the “composition of claim 1, wherein the weight ratio of chlorite:chloride is greater than 100:10.”

Patent Owner contends that the recited ratio is non-obvious because:

In view of the teachings of Mullerat, a skilled person would have been taught away from selecting a chlorite:chloride range greater than 100:10 because Mullerat discloses that “sodium chloride and potassium chloride are especially useful because of their cost and solubility” (col. 3, lines 61-62).

We have not been directed to evidence that the presence of chloride ion in a chlorite composition for intravenous use is necessary. Thus, while Mullerat may teach its presence when the composition is used for oral administration to animals, this teaching does not lead to a determination that it necessary for a pharmaceutical composition for intravenous use or in any
particular amount. McGrath II, which discloses a composition for intravenous use, expressly teaches that the chloride present in WF10 is an “inactive ingredient[ ].” FF19. Accordingly, one of ordinary skill in the art would have regarded the chloride ion as dispensable and non-critical. In regards to the amounts which are claimed, Inorganic Ventures, for example, contains only a small amount of chloride (6± 1 μg/ml) as compared to chlorite (998 ± 3 μg/ml).

Buffer and pH limitation

Rejection

Claim 1 recites that the composition comprises “(b) a phosphate buffer; and (c) a pharmaceutically acceptable excipient; wherein the composition is a sterile intravenous solution having a pH between about 7 and about 9.5.”

The Examiner cited Mullerat for its teaching of a phosphate buffered chlorite solution. RAN 5. The Examiner also cited Tissot for adjusting the pH to 7.4 of a chlorite solution with phosphate buffered saline prior to administration, and Danner for a metal chlorite solution for medical applications. Id.

The Examiner found that “it was known in the art that solutions of pharmaceuticals in general, and sodium chlorite in particular, should be adjusted to physiological pH prior to injection, as shown by Tissot.” Id. at 6.
Patent Owner’s argument

Patent Owner contends that Mullerat teaches that the pH is adjusted to 13 to provide stability over long periods of storage, and, thus, teaches away from the claimed range. Appeal Br. 12. Patent Owner also contends that the lower ranges described in Tissot are not pertinent since Tissot is not a solution for intravenous use. Id.

Patent Owner further argues that Kühne II ’285 also teaches a chlorite solution having a high pH and that lower pH can result in toxic chlorine gas. Id. at 12–13.

Patent Owner states that “None of the references cited by the Examiner even attempt to teach the skilled person how the pH could be safely lowered.” Id. at 13.

Discussion

WF10, a commercially available chlorite solution which has been used intravenously, has been described as having a pH of 12.3 (FF1) or diluted to a medicinal solution of a pH of 11.45–11.6 (FF9). The issue is whether it would have been obvious to one of ordinary skill in the art to have adjusted the pH of the chlorite solution of the claims to a pH of “about 7 and about 9.5” in a phosphate buffer.

While the intravenous chlorite solutions of WF10 described in the prior art have a higher pH than the claimed range, the Examiner provided evidence of chlorite solutions used physiologically that are within the claimed pH range and which are buffered with phosphate.
Specifically, Tissot describes a chlorite solution adjusted to pH 7.4 and diluted with a phosphate buffered saline. FF14. While Tissot’s solution is not used intravenously, it is introduced into a cellular environment of the pleural cavity of rats or in contact with cells. FF14.

Danner also describes a chlorite solution with a pH range overlapping with the claimed range. FF16. Danner teaches that the chlorite solution can be buffered with phosphate. FF17. While Danner’s chlorite composition is applied to the skin, it is used for wound healing and, thus, would be in contact with cells, as would be an intravenous solution.

Consequently, contrary to Patent Owner’s contentions, we conclude that both Tissot and Danner provide relevant guidance on how to make a chlorite solution which is placed in contact with cells for medical uses.

Additional evidence is provided by Immunokine. Immunokine is package insert for the intravenous use of WF10. While Immunokine does not specifically disclose a pH nor phosphate buffer, it indicates that the chlorite solution is diluted in a suitable diluent. FF15. Each of Tissot and Danner teach that a phosphate buffer is suitable as a diluent for in vivo use, and such a buffer is used for solutions of target pH of about 7.0 (1st Martin Decl. ¶ 13). Thus, a pH of about 7 would have been obvious when a phosphate buffer is utilized as a diluent.

While Mullerat describes a pH of 13 for storage, Mullerat also describes a suitable pH range beginning at 7.5. FF12. Thus, we do not see how a pH of 13 can be a teaching away from the claim range of 7.5 to 9, when Mullerat expressly teaches a pH as low as 7.5 as suitable for a chlorite solution. Moreover, as discussed above, the teachings in Tissot and Danner
are even more pertinent because their compositions are placed in contact with cells – as is an intravenous solution. Indeed, the claims are not restricted to a composition for intravenous use, but would read on the pharmaceutical compositions of Tissot and Danner.

With regard to the claimed pH of about 7 and above, as acknowledged by Patent Owner, an acid pH (below 7) is known to be undesirable. Appeal Br. 12–13; FF6. Consequently, the skilled worker would have reason to have utilized a chlorite composition with a pH of about 7 or above.

In sum, it would have been obvious to have made a chlorite solution with a phosphate buffer having a pH of about 7 or above because these conditions are suitable and conventional for medical applications of chlorite solutions (FF6, FF14, FF16–FF18). Moreover, Immunokine discloses diluting a chlorite solution with a “suitable” diluent prior to use intravenously (FF15), and Tissot and Danner disclosure a phosphate buffer as suitable for in vivo medical applications.

Unexpected results

A showing of “unexpected results” can be used to demonstrate the non-obviousness of the claimed invention. In re Soni, 54 F.3d 746, 750 (Fed Cir. 1995) (“One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of ‘unexpected results,’ i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.”). Patent Owner provided evidence said to establish unexpected results for the rejected claims.
Hemoglobin toxicity

The first McGrath declaration was provided during the prosecution of the patent to show that “sodium chlorite formulated according to claims 21 or 27 has reduced hemoglobin toxicity compared to WF10 when administered to human patients.” 1st McGrath Decl. ¶ 3. Claims 21 and 27 correspond to claims 1 and 2 of the issued patent.

Dr. McGrath stated in his declaration that “[h]ematologic problems including red blood cell loss (‘hemoglobinemia’) have been reported for WF10 by Veerasarn et al. (Radiotherapy and Oncology, 73 (2004) 179–185).” 1st McGrath Decl. ¶ 4. Dr. McGrath explains that hemoglobinemia is a potentially dangerous condition. Id. at ¶ 5. Dr. McGrath states that Veerasarn’s study showed “74% of patients receiving WF10 were found to have hemoglobinemia compared to 35% of control patients.” Id. at ¶¶ 7, 9, 11. In contrast, Dr. McGrath describes a clinical study performed using “[s]odium chlorite formulated according to claims 21 or 27” which “shows no evidence of causing hemoglobinemia.” Id. at ¶ 13.

Requester provided a declaration by Henrich Guntermann, M.D., to rebut the McGrath Declaration. While Dr. Guntermann challenges Dr. McGrath’s statements about the hematologic problems observed in Veerasarn (Guntermann Decl. 7–9, 13), Veerasarn explicitly states that “transient hemoglobinaemia” was “occasionally observed in patients treated with WF10.” Veerasarn 183 (Section 3.4). Dr. Guntermann did not provide adequate evidence to doubt the credibility of this statement in Veerasarn.

Dr. McGrath stated:
In the attached Figure 2, 12 ALS patients were selected at random to receive 0, 1, or 2 mg/kg sodium chlorite formulation. The results of the Phase 2 trial have not yet been unblinded, so the actual dose of sodium chlorite cannot yet be assigned to individual patients. However, as seen in Figure 2, no significant differences were observed between levels of hemoglobin before and after treatment, regardless of sodium chlorite formulation dose.

1st McGrath Decl. ¶ 14.

Dr. Guntermann testified in response that, across all the treatment protocols, “hemoglobin levels at the second post-treatment time point (labeled "HGB post 2" in Figure 2) are always below the pretreatment hemoglobin levels (labeled "HGB pre" in Figure 2), with the possible exception of patient 4 where pre and post treatment levels appear very comparable.” Guntermann Decl. ¶ 23. Because of the lack of discussion by Dr. McGrath of this apparent decline in hemoglobin levels, Dr. Guntermann found the “the scientific validity of the assertions made in the McGrath Declaration” to be undermined. Id.

While it is true that Dr. McGrath did not explain the apparent decline in hemoglobin levels, Dr. Guntermann did not provide adequate reason to doubt Dr. McGrath’s conclusion that that there was no significant change in hemoglobin level during the clinical study. At least one of these dosages was 2 mg, which is about the amount administered in the Veerasarn study. Thus, while the clinical study described by Dr. McGrath might not be completely comparable to Veerasarn as discussed by Dr. Guntermann (¶¶ 16, 17, 19), the study does have some pertinence in showing that the
administered formulation did not produce hemoglobiaemia as observed by Veerasarn (1st McGrath Decl. ¶¶ 13, 16).

Nonetheless, the data is not persuasive for at least two independent reasons.

First, as stated by Dr. Guntermann, Dr. McGrath did not disclose the formulation which was administered to the patients. He stated that the sodium chlorite was formulated according to claims 21 and 27 (the claim numbers during the prosecution which led to the ’035 patent), but these claims – now claims 1 and 2 in the issued patent – cover a range of weight ratios of chlorite to chlorate, a range of pH values, and a range of chlorite concentrations. Dr. McGrath did not disclose the chlorite:chlorate ratio, the concentration of chlorite, nor the pH of the formulation administered. Unexpected results must be “commensurate in scope with the degree of protection sought by the claimed subject matter.” In re Harris, 409 F.3d 1339, 1344 (Fed. Cir. 2005). Dr. McGrath did not explain how the results for an apparently single composition, which is not even identified, establish unexpected results for the full scope of the claim.

Second, as acknowledged by Patent Owner, it was known that sodium chlorate may cause undesirable effects when administered. FF2, FF13. Consistently, Veerasarn describes hemoglobin anaemia in patients when WF10 was administered (Veerasarn 183), which was known to comprise chlorate ion. Thus, Dr. Guntermann’s statement that “such results would not have been surprising or unexpected, given the known toxicity of chlorate and its association with hemoglobinemia” is supported by a preponderance of the evidence. Guntermann Decl. ¶ 26.
pH stability

Dr. McGrath stated in his declaration that he “observed unexpected results for the pH stability of sodium chlorite in formulations neutralized with phosphate buffer according to the claims compared to other buffers.” 2nd McGrath Decl. ¶ 5. Dr. McGrath stated that the sodium chlorite was “pH’d to 7 in the presence of water, citrate (cit), carbonate (car), borate (bor), and phosphate (phos) buffers.” Id. at ¶ 7. Dr. McGrath further stated that “As shown in Figure 1, phosphate buffer gives the greatest pH stability.” Id. at 8.

This data is not persuasive. As explained in detail in the declaration by Rainer Martin, “a skilled person working in the field in December of 2005 or December of 2006 would have expected an aqueous sodium chlorite solution to exhibit stability when buffered to a pH of 7 with a phosphate buffer.” 1st Martin Decl. ¶ 6. Dr. Martin provided a detailed scientific explanation as to why it would have been expected that a phosphate would be an effective buffer at pH 7 (id. at ¶ 13), and more effective than the other buffers tested by Dr. McGrath (id. at ¶¶ 14–17). Patent Owner did not identify a defect in Dr. Martin’s scientific reasoning. Appeal Br. 24.

Patent Owner also states “Martin's argument fails because Martin ignores the fact that the claim recites a range between about pH 7 and about pH 9.5, and because it is not obvious to one of skill in the art which buffer system would be optimal over this range.” Id. However, despite Patent Owner’s contention, the only pH studied in Dr. McGrath’s declaration was a pH of 7. 2nd McGrath Decl. ¶ 7. Patent Owner did not explain how this
result obtained at a pH 7 established that the buffering was optimal over the entire range of about 7 to 9.5.

Summary

For the foregoing reasons, the obviousness Rejection 1 of claims 1 and 12–17 is affirmed. Claims 6–11 and 18 were not argued separately and fall with claim 1.

REJECTIONS 2 AND 3

With respect to Rejections 2 and 3, Patent Owner referred to the same arguments present for Rejection 1. Appeal Br. 18, 19. We have reviewed these arguments and do not find Patent Owner in their discussion of the rejections have further distinguished the claims over the additionally cited prior art. Rejections 2 and 3 are affirmed for the same reasons as for Rejection 1.

For the purposes of any appeal pursuant to under 35 U.S.C. §§ 141-144 and 315 and 37 C.F.R. § 1.983, this Decision relies on each publication cited in all each of the rejections as defining the scope and content of the prior art. To the extent that any publication is not discussed in this Decision, we rely on the Examiner’s findings of fact. In addition, as noted above, the discussion focused on Rejection 1 because Patent Owner’s arguments centered on this rejection. However, we consider these arguments applicable to all rejections.
TIME PERIOD FOR RESPONSE

In accordance with 37 C.F.R. § 41.79(a)(1), the “[p]arties to the appeal may file a request for rehearing of the decision within one month of the date of: . . . [t]he original decision of the Board under § 41.77(a).” A request for rehearing must be in compliance with 37 C.F.R. § 41.79(b). Comments in opposition to the request and additional requests for rehearing must be in accordance with 37 C.F.R. § 41.79(c) & (d), respectively. Under 37 C.F.R. § 41.79(e), the times for requesting rehearing under paragraph (a) of this section, for requesting further rehearing under paragraph (d) of this section, and for submitting comments under paragraph (c) of this section may not be extended.

An appeal to the United States Court of Appeals for the Federal Circuit under 35 U.S.C. §§ 141–144 and 315 and 37 C.F.R. § 1.983 for an inter partes reexamination proceeding “commenced” on or after November 2, 2002 may not be taken “until all parties’ rights to request rehearing have been exhausted, at which time the decision of the Board is final and appealable by any party to the appeal to the Board.” 37 C.F.R. § 41.81. See also MPEP § 2682 (8th ed., Rev. 7, July 2008).

In the event neither party files a request for rehearing within the time provided in 37 C.F.R. § 41.79, and this Decision becomes final and appealable under 37 C.F.R. § 41.81, a party seeking judicial review must timely serve notice on the Director of the United States Patent and Trademark Office. See 37 C.F.R. §§ 90.1 and 1.983.

AFFIRMED