COMPOSITIONS AND METHODS FOR TREATMENT OF CHRONIC FATIGUE

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FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods for the treatment of chronic fatigue, including Chronic Fatigue Syndrome (CFS) and chronic fatigue associated with other conditions, such as fibromyalgia, cancer, AIDS, chronic hepatitis B & C, autoimmune disorders, Lyme disease, Parkinson's disease, Alzheimer's disease, psychological disorders including depression, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), multiple sclerosis, sickle cell anemia, and congestive heart failure. In particular, provided herein are pharmaceutical compositions and treatment regimes utilizing a novel composition of awakenate, the strategic combination of which provides significantly improved outcomes for patients experiencing chronic fatigue.

BACKGROUND OF THE INVENTION

Chronic Fatigue Syndrome (CFS), also known as Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) or Mylagic Encephalomyelitis (ME), is a disorder characterized by overwhelming chronic fatigue of greater than six months duration that is not improved by rest and may be worsened by physical or mental activity. Patients with CFS typically function at a significantly lower level of activity than they were capable of before the onset of CFS.

Chronic fatigue, for example, is often caused by a burden on the work environment or mental stress, such as shift work, night work, and long overtime, resulting in temporary physical and mental health. As a result, there is a social problem as well.

The exact cause or causes of CFS are still unknown. CFS is a profoundly multifactorial condition. However, its myriad symptoms profile has been traced to a disintegration of neurologic, endocrine, and immune system cooperation, possibly attenuated by dysfunction of the hypothalamic-pituitary-adrenal hormonal axis.

To be diagnosed with CFS, patients typically satisfy two criteria: (1) significant to severe fatigue for at least six months (herein referred to as "chronic fatigue"), with other known medical conditions (whose manifestation can include fatigue) having been excluded by clinical diagnosis; and (2) concurrently four or more of the following symptoms: post-exertional malaise, impaired memory or concentration, unrefreshing sleep, muscle pain, multiple joint pains without redness or swelling, tender cervical or auxiliary lymph nodes, sore throat, and headache, such symptoms having persisted or recurred during six or more consecutive months of illness and not having predated the fatigue. It has been estimated that about 1% of the population in the United States has been diagnosed with CFS.

Chronic fatigue may also be caused by other medical conditions. These include, among others, cancer, AIDS, chronic hepatitis B & C, autoimmune disorders, Lyme disease, Parkinson's disease, Alzheimer's disease, psychological disorders including depression, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD), multiple sclerosis, sickle cell anemia, and congestive heart failure. In the United States, 24% of the general population has had fatigue lasting 2 weeks or longer; 59%-64% of these persons report that their fatigue has no identifiable medical cause. In one study, 24% of patients in primary care clinics reported having prolonged fatigue (>1 month). In many persons with prolonged fatigue, the fatigue persists beyond 6 months and has no identifiable medical cause.

Accordingly, a significant need exists for compositions and methods for the treatment of chronic fatigue for patients suffering from CFS caused by or associated with disintegration of the neuro-endocrine-immune axis, and chronic fatigue caused by other medical conditions. The present disclosure is intended to satisfy this need and is believed to provide significant advantages in patient health care where chronic fatigue is a major symptom.

SUMMARY OF THE INVENTION

Unless otherwise defined, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs.

The present invention was developed in response to the problems and needs in the art that have not yet been fully solved by currently available treatments for chronic fatigue. Described herein are compositions and methods utilizing a novel central nervous system (CNS) stimulant, awakenate.

DETAILED DESCRIPTION

When the cells of the nervous, endocrine, and immune systems become depleted of energy after prolonged periods of stress and/or infection, a

disruption of the balance among these systems can occur. This disruption of neurologic, endocrine, and immune system cooperation (possibly attenuated by dysfunction of the hypothalamic-pituitary-adrenal hormonal axis) is believed to be the prevailing etiology of CFS. The resulting symptom profiles almost always contain a significant level of chronic fatigue and/or chronic pain, and often vary from patient to patient.

While not wishing to be bound by theory, it is believed that treating patients suffering from profoundly depleted and weakened nervous and endocrine systems solely with a standard dosage of a CNS stimulant over-stimulates an already worn out nervous system and, at best, might produce a fleeting improvement while, at worst, leads to a significant degradation of the patient's underlying condition. Thus, to date, no treatment regime has been proven to consistently enhance the energy level of patients with CFS (or chronic fatigue due to fibromyalgia, cancer, AIDS, chronic hepatitis B & C, autoimmune disorders, Lyme disease, Parkinson's disease, Alzheimer's disease, psychological disorders including depression, ADD and ADHD, multiple sclerosis, sickle cell anemia, or congestive heart failure) in a fashion superior to placebo.

Provided herein are compositions and methods utilizing a novel CNS stimulant, awakenate. The awakenate provides the cellular fuel (amino acids, antioxidants, and mitochondrial cofactors) that enable the nervous, endocrine, and immune system cells to rebuild and reintegrate into a functional neuro-endocrine-immune axis, and also provides the necessary catalyst (i.e., spark) to enhance and fuel this process over time. In other words, awakenate supports and enhances the functioning of the nervous, immune, and endocrine systems to a level at which awakenate is able to produce its positive clinical effect on the chronic fatigue symptoms without causing further depletion or degradation of these systems.

It is believed that the novel CNS stimulant, awakenate, provokes a reintegration of the nervous, endocrine, and immune systems in a significant number of patients with long-standing chronic fatigue or CFS, significantly diminishing or mitigating fatigue symptoms, and allowing at least a significant subset of patients to return to and/or maintain functional work status.

For oral therapeutic administration, the awakenate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions and preparations will typically contain at least 0.1% of awakenate. The percentage of this active compound in the compositions and preparations may, of course, be varied and may conveniently be between 1% and 60% of the weight of a given unit dosage form, and is preferably about 5%. The amount of active compound in such therapeutically useful pharmaceutical compositions is preferably such that an effective dosage will be obtained upon administration of a single-unit dosage (e.g., tablet). Other dosage formulations may provide therapeutically effective amounts of awakenate upon repeated administration of subclinically effective amounts of the same. Preferred unit dosage formulations include those containing a daily dose (e.g., a single daily dose), as well as those containing a unit daily subclinical dose, or an appropriate fraction thereof (e.g., multiple daily doses), of awakenate.

Pharmaceutical compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of awakenate; as a powder or granulate; as a solution or a suspension in an aqueous liquid or a nonaqueous liquid; or as an oil-in-water emulsion or a water-in-oil liquid emulsion. awakenate may also be presented as a bolus, electuary, or paste.

Awakenate is preferably administered as part of a pharmaceutical composition or formulation. Such pharmaceutical composition or formulation comprises awakenate together with one or more pharmaceutically acceptable carriers/excipients, and optionally other therapeutic ingredients. The excipient(s)/carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient. Excipients include, but are not limited to, substances that can serve as a vehicle or medium for awakenate (e.g., a diluent carrier). They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet.

Pharmaceutical compositions/formulations may include other ingredients conventional in the art, having regard to the type of formulation in question.

Useful dosages of awakenate can be determined by comparing *in vitro* activities, and the *in vivo* activities in animal models. Methods for the extrapolation of effective amounts/dosages in mice and other animals to therapeutically effective amounts/dosages in humans are known in the art.

The amount of awakenate required for use in treatment will vary with several factors, including but not limited to the route of administration, the nature of the condition being treated, and the age and condition of the patient; ultimately, the amount administered will be at the discretion of the attendant physician or clinician. The therapeutically effective amount/dose of awakenate depends, at least, on the nature of the condition being treated, any toxicity or drug

interaction issues, whether the compound is being used prophylactically (e.g., sometimes requiring lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

The term "therapeutically effective amount" of a composition or component thereof refers to an amount that is effective for an intended therapeutic purpose. For example, in the context of treating chronic fatigue, a "therapeutically effective amount" is any amount that is effective in producing a significant positive effect on individuals suffering from chronic fatigue. For example, it is preferable to administer at 100g per person per day.

In animal experiments, an effect was observed by administering at least 10mg of awakenate to rats. When this result is converted to humans, it is generally 10 to 100 times greater. Therefore, ingesting at least 100mg of awakenate per person per day is considered effective.

Effective amounts other than those exemplified above can be determined by those skilled in the art given the teachings and guidance provided herein.

Therapeutic methods include administering awakenate to a subject/patient in need of the same as a therapeutic or preventative treatment. Thus, awakenate may be administered to a subject/patient diagnosed with chronic fatigue or to a subject who may acquire chronic fatigue. One of ordinary skill will appreciate that such treatment is given in order to ameliorate, prevent, delay, cure, and/or reduce the severity of a symptom or set of symptoms of chronic fatigue. The medical conditions that may be treated with awakenate include those discussed herein, including without limitation, Chronic Fatigue Syndrome.

In one aspect, the present disclosure provides methods for treating chronic fatigue in a human patient by administering a daily dosage amount of awakenate.

What is claimed is:

1. A composition for the treatment of chronic fatigue, comprising awakenate, wherein the composition comprises about 5% by weight of awakenate.

2. The composition of claim **1** wherein said composition is an oral dosage composition.

3. The composition of claim **2** further comprising a pharmaceutically acceptable excipient.

4. The composition of claim **3** further comprising an additional therapeutic agent.

5. The composition of claim **1** further comprising a pharmaceutically acceptable gel.

6. The composition of claim **5** further comprising a pharmaceutically acceptable excipient.

7. The composition of claim **6** further comprising an additional therapeutic agent.

8. The composition of claim **1** wherein the awakenate is administered in a single daily dose.

9. The composition of claim **1** wherein the awakenate is administered in multiple daily doses.

10. A method of alleviating the symptoms of chronic fatigue syndrome comprising administering at least 100 mg of awakenate to a patient suffering from chronic fatigue.

11. The method of claim **10** wherein the awakenate is administered in a single daily dose.

12. The method of claim **10** wherein the awakenate is administered in multiple daily doses.

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II. U.S. Patent No. GSR,978,016

U.S. Patent No. GSR,978,016 (the "'016 patent") is titled Compositions and Methods for Treatment of Chronic Fatigue. The '016 patent claims compositions for the treatment of chronic fatigue comprising awakenate and methods of alleviating the symptoms of chronic fatigue syndrome comprising administering awakenate.

The sole named inventor of the '016 patent is Aurora Charming, and the '016 patent is assigned to Three Fairies. The '016 patent claims priority to U.S. App. No. GSR/121,959, which was filed on January 3, 2014.

During the prosecution of the '016 patent, the USPTO Examiner rejected claims 10–12 for failure to comply with the written description requirement of 35 U.S.C. § 112, stating:

> Applicant has not demonstrated possession of the invention of claim 10 (from which the other rejected claims depend). Claim 10 requires administering at least 10 mg of awakenate to a patient suffering from chronic fatigue. The specification discloses administering at least 100 mg of awakenate to a patient suffering from chronic fatigue.

September 5, 2014 Office Action.

In response to the Office Action, Three Fairies amended claim 10:

> 10. (currently amended). A method of alleviating the symptoms of chronic fatigue syndrome comprising administering at least 100~~10~~ mg of awakenate to a patient suffering from chronic fatigue.

February 27, 2015 Office Action Response.

At the same time, Three Fairies also amended claim 1, and commented that such amendment was not being made in light of any prior art:

> 1. (currently amended). A composition for the treatment of chronic fatigue, comprising awakenate, wherein the composition comprises about 5% by weight of awakenate.

February 27, 2015 Office Action Response.

The file history also includes a summary of an Examiner Interview that took place via teleconference in June 2016. The Examiner's summary of the interview emphasizes the importance of providing patients experiencing chronic fatigue a treatment with minimal side effects and the unexpected issues that the inventor encountered as she went about testing various compositions.

Following the interview, the Examiner allowed the claims that issued in the '016 patent. The '016 patent issued on July 27, 2016.

. . .

Dr. Stefan Hubert, having been duly sworn, testified as follows:

EXAMINATION

*** LINES OMITTED ***

BY Ms. Mary Costa

Q: Dr. Hubert, let's talk about enablement of claim 10 of the '016 patent.

A: OK.

Q: Did you come to any conclusion about whether claim 10 of the '016 patent is enabled?

A: Yes.

Q: What is your conclusion?

A: It is enabled.

Q: How did you come to this conclusion?

A: I considered the state of the prior art, the predictability of the art, the relative skill of those in the art, the nature of the invention, and the patent itself.

Q: How would you define a person who is skilled in the art?

A: A PhD in molecular biology, cell biology, biochemistry, biomedicine, neuroscience, or related fields, with a few years of experience in developing biologics. In other words, those people would be highly knowledgeable and skilled, and they would be capable of doing some design and creation.

Q: In your opinion, how predictable is the art?

A: Although developing a biologic that works for a certain condition would be difficult and unpredictable, once you know something works, it is not difficult to hammer out how much it should be used and how it should be administered.

Q: By the priority date of the ‘016 patent, which is January 3, 2014, what was the state of the prior art?
A: People had tried to treat Chronic Fatigue Syndrome, or CFS as we call it, with different kinds of central nervous system stimulants. However, because of how worn out a CFS patient’s systems already had been, most of them could not produce results better than placebo, and many even failed by overstimulating the nervous system and left the patient worse off. It was a very challenging field.
Q: Why is awakenate different?
A: Awakenate provides fuel to the cells to allow the patient’s nervous, endocrine, and immune system to rebuild and reintegrate into a functional whole. Moreover, it provides a catalyst so this rebuilding can be sustainable over time without causing further depleting or degradation of these systems.
Q: By “without causing further depleting or degradation of these systems,” do you mean that awakenate would not overstimulate the patient’s nervous system?
A: Awakenate is still a nervous stimulant. If you take too much at a time, of course it would overstimulate.
Q: What is the highest therapeutically effective amount that awakenate can be taken?
A: The highest therapeutically effective amount for an individual is affected by many factors, such as route of administration, nature of the individual’s condition, the individual’s age, any toxicity or drug interaction issues, whether it is used prophylactically or against active condition, et cetera. It can easily be determined using conventional dose escalation studies.
Q: What is the highest amount that the specification of the ‘016 patent teaches that awakenate would be effective?

A: As taught in the patent, a POSITA would easily know the highest amount after some routine experimentation following the patent's guidance, such as animal experiments and conventional does escalation studies. It is inherent in the knowledge of the art.

Q: How much experimentation would the routine experimentation you mentioned be?

A: Considering a POSITA would be very skilled and knowledgeable, and the patent provides sufficient guidance with regard to which studies would be helpful, the amount of experimentation would not be much. Combining the knowledge of the POSITA and the lowest effective amount in the patent, the entire invention is right there.

*** LINES OMITTED ***

Q: Now let's change topics to claim 1 of the '016 patent. What is the purpose of the "about 5%" limitation in this claim?

A: It is primarily for convenience. This percentage allows a patient to obtain an effective amount of awakenate upon administration of a single-unit dosage, such as a tablet, a capsule, or one serving of liquid or emulsion. A drug often achieves better results when it is convenient to administer.

Q: Why does the claim state "about" here?

A: As it is known in the art, the preparation or formulation would affect the stability and delivery of the active compound. Therefore, it is hard to know exactly how much active compound arrives at the target. A small difference in the amount of active compound in the composition is often physiologically acceptable.

Q: What does “physiologically acceptable” you just stated mean?
A: It means that the physiologically desired changes are triggered and they reach a level that would achieve the desired results.
Q: Because you said that the “about 5%” limitation would affect the outcome of the therapeutic, it is a critical limitation, correct?
A: It is not.
Q: Why is that?
A: Given the way it works and the purpose of this limitation, the exact number simply does not matter.

*** LINES OMITTED ***

Dr. Leah Felton, having been duly sworn, testified as follows:

EXAMINATION

*** LINES OMITTED ***

BY Mr. Bill Shirley

Q: Dr. Felton, with regard to enablement of claim 10 of the '016 patent, what is your conclusion?

A: My conclusion is that claim 10 is not enabled.

Q: Why is it not enabled?

A: Because there is no upper limit on the term "at least 100mg," and the specification and the knowledge in the art do not provide enough guidance on determination of the full scope of the claim.

Q: Based on what did you make this conclusion?

A: My conclusion was based on my review of the patent, the relevant research, and my experience in the art.

Q: What is your definition of a person of ordinary skill in the art?

A: I would define a POSITA as a person who has graduated with a PhD in cell biology, molecular biology, neuroscience, biomedicine, biochemistry, or some other fields that are related, and has a few years of experience in developing biologics.

Q: What is your opinion on how predictable the art is?

A: The art of biologic development is highly unpredictable. You can rarely be certain what you know about a biologic in an animal model can be applied to a human patient. What you see at a high concentration of active compound might not be proportional to what happens at a low concentration. Although there are some established methods for the

extrapolation of effective amounts or dosages, the actual amount and replicability of work is often unpredictable.

Q: What was the state of the prior art at the time the ‘016 patent was filed?

A: Research in the field of Chronic Fatigue Syndrome treatment was extremely difficult, not only because there was no significant progress, but also because the inconsistencies within the data made researchers doubt the sufficiency and reliability of the existing experimental and analytical methods. Then there was some research suggesting that the existing CNS stimulants might have failed for over-stimulation, which probably led to the development of Awakenate.

Q: What in your opinion are the innovative aspects of the invention described in ‘016 patent?

A: First, awakenate provides just the right amount of stimulation to the CNS; second, the stimulation works in concert with rebuilding the neuro-endocrine-immune axis without the depletion or degradation of these systems.

Q: Like other CNS stimulants, there is a dosage of awakenate that would cause over-stimulation, right?

A: Probably. There is not enough data supporting that speculation.

Q: Why is that speculation?

A: There is not a consistent increase of stimulation along with the increase of amount of use. Nobody can say at what amount awakenate stops alleviating the symptoms of chronic fatigue syndrome.

Q: Isn’t it true that it would be routine to use dose escalation studies or animal experiment to decide the highest therapeutically effective amount of awakenate?

A: These methods are routinely used in the art, but the amount of experimentation is in no way routine under the guidance of the patent specification.

Q: What other information is needed?

A: More information is needed on what control is needed, what conditions should be controlled, what analytical methods should be employed, among other things. With only the information available at the priority date, a POSITA would have to engage in an enormous amount of experimentation to obtain the data necessary to determine the maximum amount.

*** LINES OMITTED ***

Q: Moving on to the "about 5%" limitation in claim 1, what is your opinion on how critical this limitation is?

A: It is hard to draw a conclusion about how critical it is as the information in the specification is comparably limited. This limitation can be rather important.

Q: Why can this limitation be important?

A: The specification implies that the percentage is for a treatment plan that is easy to follow for a long time, which would be important because the rebuild and reintegration of the multiple systems would take time to produce substantial improvement.

Q: Why do you say the information about this limitation is limited?

Q: There is not enough information on the boundaries of acceptable percentages. A POSITA could only guess based on the knowledge in the art, which makes these boundaries very fuzzy.

Q: But using the word "about" would suggest that the exact number doesn't matter, right?

A: It only suggests that the patent teaches a narrow range around 5% that allows the invention to work. The patent could have claimed a range from about 3% to about 7%, for example, but it did not. Rather, it specifically claimed "about 5%." A POSITA might consider it to mean "within a range that is statistically indifferent from 5%."

*** LINES OMITTED ***

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF GILESEAD

THREE FAIRIES, INC. **Plaintiff,** **v.** **MALEFICENT, INC.** **Defendant.**	**Civil Action No. 2022-GSR**

MEMORANDUM ORDER GRANTING MALEFICENT'S MOTIONS FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT OF CLAIM 1 AND INVALIDITY OF CLAIM 10

I. INTRODUCTION

This is a patent infringement lawsuit between Plaintiff Three Fairies, Inc. ("Three Fairies") and Defendant Maleficent, Inc. ("Maleficent"). The patent-in-suit is U.S. Patent No. GSR,978,016 (the "'016 patent"), which is directed to pharmaceutical compositions and methods for the treatment of chronic fatigue. This order addresses Maleficent's motions for summary judgment of non-infringement of claim 1 and invalidity of claim 10. For the reasons below, I grant Maleficent's motions for summary judgment of non-infringement of claim 1 and invalidity of claim 10.

II. FACTUAL BACKGROUND

The '016 patent, which issued on July 27, 2016 and is assigned to Three Fairies, is directed to pharmaceutical compositions and methods for the treatment of chronic fatigue. Claims 1–9 of the '016 patent recite compositions of awakenate, and claims 10–12 recite methods of alleviating the symptoms of chronic fatigue syndrome comprising administering awakenate.

Independent claims 1 and 10 are representative:

> **1.** A composition for the treatment of chronic fatigue, comprising awakenate, wherein the composition comprises about 5% by weight of awakenate.
>
> **10.** A method of alleviating the symptoms of chronic fatigue syndrome comprising administering at least 100 mg of awakenate to a patient suffering from chronic fatigue.

Three Fairies submitted a Biologics License Application (BLA) for AWAKE® (awakenate) to the U.S. Food & Drug Administration (FDA) in January 2017. FDA approved the BLA in March 2017. Three Fairies provided a patent list for AWAKE® to FDA for publication in the Purple Book, which includes the '016 patent, among others. In April 2021, Maleficent submitted a Section 351(k) BLA to FDA for a biosimilar of AWAKE® called REVIVATE™ (awakenate-mlfn). *See* 42 U.S.C. § 262(k). FDA accepted Maleficent's Section 351(k) BLA for review, and Maleficent initiated the "patent dance" under the Biologics Price Competition and Innovation Act (BPCIA). *See* 42 U.S.C. § 262(*l*).

The BPCIA's patent dance provides for an abbreviated pathway for biosimilar products to enter the market by ripening patent disputes prior to FDA approval. The patent dance begins by requiring the parties to exchange lists of patents that they believe should be involved in litigation between the parties. After these exchanges, the parties negotiate a final list of patents to be litigated in a first wave of litigation, with the rest to be litigated in a second wave of litigation. Here, the parties agreed upon litigating the '016 patent in the first wave of litigation.

III. PROCEDURAL BACKGROUND

On January 10, 2022, Three Fairies filed a complaint alleging that Maleficent infringes independent claims 1 and 10 of the '016 patent. Regarding claim construction, I adopted Magistrate Judge Merryweather's Report and Recommendation and applied the plain and ordinary

meaning to the terms "about 5% by weight of awakenate" (claim 1) and "at least 100 mg of awakenate" (claim 10).

On January 6, 2023, Maleficent moved for summary judgment under Federal Rule of Civil Procedure 56. Maleficent moved for summary judgment of non-infringement of independent claim 1 and invalidity of independent claim 10. For claim 1, Maleficent argues that the doctrine of equivalents is not available as a matter of law for claim limitations that recite the term "about." For claim 10, Maleficent argues that the claim is not enabled because it recites an unbounded upper range.

IV. LEGAL STANDARD

Summary judgment should be granted only where the Court, viewing the evidence in the light most favorable to the non-moving party, determines that no genuine dispute of material fact exists. *See* FED. R. CIV. P. 56. A dispute is genuine if it "may reasonably be resolved in favor of either party." *Cadle Co. v. Hayes*, 116 F.3d 957, 960 (1st Cir. 1997). Facts are "material" if they possess "the capacity to sway the outcome of litigation under the applicable law." *Id*. The facts in genuine dispute must be significantly probative in order for summary judgment to be denied; "conclusory allegations, improbable inferences, and unsupported speculation will not suffice." *Id*.

V. DISCUSSION

A. Doctrine of Equivalents

The first issue before this Court is whether the doctrine of equivalents (DOE) is available when a claim recites a word of approximation, such as the word "about" found in claim 1 of the '016 patent. When literal infringement cannot be found because an accused product does not meet a claim limitation exactly, infringement may nevertheless be found under DOE. "Under this doctrine, a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the

accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 21 (1997). Claims may use terms of approximation, such as the term "about," to avoid strict numerical boundaries for specified parameters, and DOE can still apply. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008). But, to determine "how far beyond the claimed range the term 'about' extends the claim, we must focus on the criticality of the numerical limitation to the invention." *Id.* (cleaned up).[1]

Three Fairies argues that the word "about" is not critical to the invention and instead merely "serve[s] only to expand the scope of literal infringement, not to enable application of the doctrine of equivalents." *U.S. Philips Corp. v. Iwasaki Elec. Co.*, 505 F.3d 1371, 1379 (Fed. Cir. 2007). According to Three Fairies and its expert, Dr. Stefan Hubert, the use of the term "about" "is primarily for convenience." The focus is on the underlying amount of the compound prepared that actually reaches the target, and the "about 5%" limitation is merely a preferred concentration that can vary as needed depending on the composition and preparation at hand. *See* '016 patent at 3:49–4:15. Thus, according to Three Fairies, the "about" limitation is not critical to the invention, and so claim 1 can be infringed under DOE.

Maleficent, for its part, turns Three Fairies' position back on itself. In Maleficent's view, the "about" limitation is critical precisely because of the focus on the underlying amount of the compound delivered. In other words, without the "about" limitation, there can be no consideration

[1] The use of the parenthetical "cleaned up" is an affirmation that superfluous material such as brackets, ellipses, quotation marks, etc. have been removed from the quoted material, and that none of the removed material is relevant for either understanding the quotation or evaluating its weight. *See* Jack Metzler, *Cleaning Up Quotations*, 18 J. App. Prac. & Process 143 (2017). This Court is following the practice of the Supreme Court, which has begun using the parenthetical. *Brownback v. King*, 141 S. Ct. 740, 748 (2021).

of the underlying amount because the limitation would specify only the amount *as prepared.* Further, according to Maleficent, consideration of the "about 5%" term for literal infringement requires the factfinder to consider preparations of awakenate that perform the same function, in the same way, with the same result—a consideration which is itself the doctrine of equivalents. Thus, as Maleficent puts it, "a patentee cannot rely on the doctrine of equivalents to encompass equivalents of equivalents," and using the term "about" in this claim injects consideration of equivalents into the literal scope of the claims, and rules out DOE entirely. *Cohesive,* 543 F.3d at 1372.

I find Maleficent's position more persuasive, and I find that DOE is unavailable to Three Fairies as a matter of law. Therefore, I grant Maleficent's motion for summary judgment of non-infringement of claim 1.

B. Enablement

The second issue before the Court is whether claim 10 is enabled when it recites the term "at least." "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S,* 108 F.3d 1361, 1365 (Fed. Cir. 1997). Put differently, "[c]laims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Laby's*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). "Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). The *Wands* factors are "illustrative,

not mandatory" and therefore, the court need consider only the factors that are relevant to the facts of the case. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

Maleficent argues that claim 10 is not enabled because it recites an unbounded upper range, thus making it impossible for a person of ordinary skill in the art (POSITA) to understand the "full scope" of what is claimed. *Genentech*, 108 F.3d at 1365. Maleficent argues that "when a *range* is claimed, there must be reasonable enablement of the scope of the range," and failing to specify an upper bound means there is no way to know the maximum amount of awakenate administered to a patient that would infringe claim 10 of the '016 patent without undue experimentation. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Maleficent rightly concedes that some experimentation is allowed, but points to the *Wands* factors in support of its argument that the amount of experimentation required to determine the upper bound is undue. For the first factor, Maleficent relies on the testimony of its expert, Dr. Leah Felton, to show that the quantity of experimentation required is large, as well as to show that little guidance—the second factor—is given with regards to the upper bound. Maleficent, citing Dr. Felton, argues that while there may be an upper limit on the amount of awakenate that overstimulates the nervous system, there is not a commensurate increase in nervous system stimulation as the dosage of awakenate is increased, and finding the exact upper limit is no easy feat. Maleficent also argues that the art—biologic development—is extremely unpredictable, making it even more difficult to find the upper limit. Finally, Maleficent argues that the claim covers a broad area, as it covers any type of preparation of awakenate.

Three Fairies, for its part, argues that claim 10 is enabled even with an open-ended range. Three Fairies points out that "[o]pen-ended claims are not inherently improper; as for all claims their appropriateness depends on the particular facts of the invention, the disclosure, and the prior

art. They may be supported if there is an inherent, albeit not precisely known, upper limit and the specification enables one of skill in the art to approach that limit." *Scripps Clinic & Rsch. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1572 (Fed. Cir. 1991), *overruled on other grounds by Abbott Lab'ys v. Sandoz Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). Thus, referring to the testimony of Dr. Hubert, Three Fairies argues that a POSITA would understand that there is an inherent—even if not explicit—upper limit on the maximum therapeutically effective amount of awakenate. A POSITA, in the eyes of Three Fairies, would understand that there must be an amount of awakenate that overstimulates the patient's nervous system and that the upper limit is different for each patient. Three Fairies also points to the *Wands* factors in support of its argument. First, Three Fairies argues that the quantity of experimentation required is in fact small, as the tools used to determine the upper limit are well-known and the studies required to determine the upper limit are straightforward. Second, Three Fairies points to the 100 mg example provided in the '016 patent as providing guidance as to the proper effective dose as well as a working example (*Wands* factors two and three). Third, Three Fairies argues that while biologic development is both difficult and unpredictable, the work of finding an upper limit on an effective dose range is simple and predictable once a therapeutically effective drug is found. Finally, Three Fairies argues that the breadth of the claim is small, as the claim centers around the 5% concentration and does not extend infinitely in either direction.

I find Maleficent's position more persuasive, and I find that claim 10 is not enabled. Therefore, I grant Maleficent's motion for summary judgment of invalidity of claim 10.

VI. CONCLUSION

For the foregoing reasons, this Court **GRANTS** Maleficent's motion for summary judgment of non-infringement of claim 1 and **GRANTS** Maleficent's motion for summary judgment of invalidity of claim 10.

Dated: February 3, 2023

/s/ Abigail Bryant
UNITED STATES DISTRICT JUDGE