Paper No. _____

Filed on behalf of: Insys Development Company, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Insys Development Company, Inc.,
Petitioner

v.

GW Pharma Limited,
Patent Owner

Case No. Unassigned
Patent No. 9,066,920

Petition for *Inter Partes* Review of U.S. Patent No. 9,066,920

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Ex. 1011: Ames *et al*, *Anticonvulsant effect of cannabidiol*, South African Medical Journal 69:14 (1986).

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Ex. 1025: Zuardi *et al*, Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action, Rev Bras Psiquiatr., 30(3): 271-80 (2008).

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Ex. 1027: Wallace *et al.*; Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects, Eu J Pharmacol 428: 51-57 (2001).

Ex. 1028: Castel-Branco *et al*; The Maximal Electroshock Seizure (MES) Model in the Preclinical Assessment of Potential New Antiepileptic Drugs, Methods Find Exp Clin Pharmacol 2009, 31(2); 101-106.

Ex. 1029: Cortesi *et al*, Potential therapeutical effects of cannabidiol in children with pharmacoresistant epilepsy, Med Hypotheses. 2007;68(4):920-1. Epub 2006 Nov 16.

Cases

Statutes

I. INTRODUCTION

Insys Development Company, Inc. ("Insys" or "Petitioner") petitions for *Inter Partes* Review ("IPR"), seeking cancellation of all claims of U.S. Patent No. 9,066,920 to Whalley *et al.* ("the '920 patent") (**Exhibit 1001**) assigned to GW Pharma Limited ("GW Pharma") and Otsuka Pharmaceutical Co., Limited ("Otsuka"). For the purposes of this Petition, Insys will refer to "GW Pharma" as Owner of the '920 patent.

II. OVERVIEW

All of the claims of the '920 patent should be canceled. They are directed to methods of treating partial seizure comprising administering cannabidiol (CBD) to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg. (**Exhibit 1001**, at 15:5-8).

"Partial seizure" and "generalized seizure" are subsets of a condition called "seizures." The use of CBD to treat seizures was well known prior to the invention, as documented in the '920 patent itself, as well as many prior art references. (The '920 patent, **Exhibit 1001**, at 1:52-67; 2:1-12; Cunha *et al*, **Exhibit 1004**, at Abstract; Ames *et al*, **Exhibit 1011**). It was also known that CBD was successfully used to treat a subset of "partial seizures," namely secondary generalized seizures. (Cunha *et al*, **Exhibit 1004**, at 183).

The only difference between the subject matter of the '920 patent and the prior art is that the prior art does not explicitly disclose administering the recited daily dosage of at least 400 mg of CBD for the treatment of partial seizure. However, it would have been obvious to a person having ordinary skill in the art ("PHOSITA") to treat partial seizures with CBD at the claimed amount because it was well known that CBD was extremely well tolerated in humans, at doses of up to 600 mg (**Exhibit 1012**, page 445) and because it was well within a skill in the art to optimize a treatment dosage. (**Exhibit 1002**, ¶ 48).

Moreover, prior art discloses that dosages of 600 mg of CBD were safely administered to humans without any negative side effects. The prior art also discloses that there is a large overlap between the drugs that treat generalized seizures and partial seizures. Professor Marson, a preeminent expert in the field of treating seizures, states that there was a reasonable likelihood that CBD would be an effective treatment for partial seizures at a daily dosage 200-300 mg and that this dosage could be safely increased to arrive at the optimal dosage. (**Exhibit 1002**, ¶ 64).

Further, Professor Benet, a preeminent expert in the field of pharmacology and pharmacokinetics, stated that in his opinion, the skilled person, familiar with the literature relating to CBD for the treatment of seizures explains that it would be obvious for a person having ordinary skill in the art ("PHOSITA") to increase the

daily dose of CBD up to 1500 mg for the treatment of partial seizures. (**Exhibit 1003**, ¶ 37).

There is absolutely nothing in the '920 patent to suggest that the use of a higher dose of CBD is unexpected or otherwise not obvious.

The United States Patent and Trademark Office ("USPTO" or "PTO") Examiner allowed the claims to issue based, in a large part, on a mistaken belief that one of the prior art references, which is one of GW Pharma's own patent applications, teaches away from the claimed invention because it allegedly teaches that daily dosages of up to 120 mg of a cannabinoid are a problem to be overcome. (**Exhibit 1005**, paragraph bridging pages 2 and 3). However, the reference in question (WO 02/064109 or "WO '109") does not teach away from the invention. Instead, WO '109 teaches how to solubilize large doses of CBD. (**Exhibit 1006**, page 5, ll1-6). WO '109 does not teach how to minimize the amount of CBD (or any other cannabinoid), but rather how to choose a co-solvent in order to reduce the amount of ethanol needed to solubilize a cannabinoid. If anything, WO '109 suggests **higher** doses of CBD since it teaches that more than 90% of an ingested cannabinoid is removed due to the metabolic "first pass effect." This is supported by an expert declaration by Professor Leslie Benet, a preeminent pharmacologist. (**Exhibit 1003**, ¶¶ 41-47).

To summarize, the prior art unmistakably renders the claimed methods of treatment of partial seizures comprising administering specific amounts of CBD obvious.

III. STANDING (37 C.F.R. §42.104(A)); PROCEDURAL STATEMENTS

Petitioner certifies that: (1) the '920 patent is available for IPR and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '920 patent. This Petition is filed in accordance with 37 C.F.R. §42.106(a). A Power of Attorney is filed concurrently herewith. The required fee is paid via USPTO Deposit Account 23-0785. The Office is authorized to charge fee deficiencies and credit overpayments to the same Deposit Account.

IV. MANDATORY NOTICES (37 C.F.R. §42.8(a)(1))

Real Party-In-Interest (37 C.F.R. §42.8(b)(1)) is Insys Development Company, Inc.

Related Matters (37 C.F.R. §42.8(b)(2)): None.

Designation of Lead and Back-Up Counsel (37 C.F.R. §42.8(b)(3)):

Lead Counsel	Back-Up Counsel

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Notice of Service Information (37 C.F.R. §42.8(b)(4)): Please direct all correspondence regarding this Petition to Counsel at the above addresses. Petitioner consents to service by email at the addresses above.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. §42.22(A))

Petitioner requests IPR and cancellation of claims 1-13. Petitioner's full statement of the reasons for the relief requested is set forth in detail in Section XII of this Petition.

VI. PERSON HAVING ORDINARY SKILL IN THE ART ("PHOSITA")

A person having ordinary skill in the art ("PHOSITA") is a hypothetical person who is presumed to be aware of all the pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the subject matter of the '920 patent, a PHOSITA would typically have had an M.D. or a Ph.D. in pharmacology, chemistry, biochemistry, neurology, or in a related field in the biological or chemical sciences. A PHOSITA would also be

familiar with the 1981 International League Against Epilepsy (ILAE) classification of seizures and be up-to-date on the developments in the field of treatment of seizures.

VII. THE CLAIMS

The claims of the '920 patent recite methods of treatment of partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

Claim 1 is the only independent claim which is directed to a method of treatment of partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

Dependent claim 2 specifies the daily amount of CBD to be from 400 to 800 mg.

Dependent claims 3-5 and 10-13 require a co-administration of tetrahydrocannabivarin (THCV).

Dependent claim 6 specifies that the CBD is present as a plant extract.

Dependent claim 7 specifies that the plant extract comprises less than 5% by weight of tetrahydrocannabinol (THC) as a percentage of any cannabinoids present in the plant extract.

Dependent claim 8 specifies that the plant extract comprises less than 1% by weight of THC as a percentage of any cannabinoids present in the plant extract.

Dependent claim 9 specifies that the CBD is present as a pure or isolated cannabinoid.

VIII. STATE OF THE ART

A. SEIZURES CLASSIFICATION BY INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE).

It is very important to understand what seizures are and how seizures were classified by the International League Against Epilepsy (ILAE) as of July 3, 2009, the effective date of the '920 patent.

1. WHAT ARE SEIZURES

Insys has retained Professor Marson, a pre-eminent expert in the field of seizures as can be seen in his Curriculum Vitae (CV). Professor Marson first clarifies and defines seizures in the Marson Declaration. As he explains, a seizure is the manifestation of an abnormal, hypersynchronous discharge of a population of cortical neurons. This discharge may produce subjective symptoms or objective signs, in which case it is a clinical seizure, or it may be apparent only on an electroencephalogram (EEG), in which case it is an electrographic (or subclinical) seizure. (**Exhibit 1002**, ¶ 14).

The diagnosis of a particular seizure type, and of a specific type of epilepsy (epilepsy syndrome), dictates the diagnostic workup of these patients and their initial therapy. (**Exhibit 1002**, ¶ 15).

2. ILAE CLASSIFICATION

By July 2009, the earliest priority date of the '920 patent, seizures were identified according to a classification developed by a commission organized by the International League Against Epilepsy (ILAE). The ILAE is the world's preeminent association of physicians and other health care professionals. As Professor Marson explains, by July 2009, the ILAE classification was the best classification available and was widely referred to in standard medical textbooks and widely used in routine clinical practice and in the scientific literature. (**Exhibit 1002**, ¶ 16).

Although the ILAE classification was first implemented in 1969, it was updated many times since its inception. The ILAE classification relevant to the '920 patent was published in 1981 by Dreifuss *et al* (**Exhibit 1007**). The most recent update prior to the priority date of the '920 patent was in 2006. (**Exhibit 1009**). However, the 2006 update did not materially change the distinction between generalized seizures and partial seizures. (**Exhibit 1002**, ¶ 16). In any event, the '920 patent does not refer to the 2006 update.

The '920 patent intended to follow the ILAE classification system as is evident from the following passage:

> Neuronal activity is a prerequisite for proper brain function. However, disturbing the excitatory-inhibitory equilibrium of neuronal activity may induce epileptic seizures. These epileptic seizures can be grouped into two basic categories: partial and generalised seizures. Partial seizures originate in specific brain regions and remain localised--most commonly the temporal lobes (containing the hippocampus), whereas generalised seizures appear in the entire forebrain as a secondary generalisation of a partial seizure (McCormick and Contreras, 2001, Lutz, 2004). This concept of partial and generalised seizure classification did not become common practice until the International League Against Epilepsy published a classification scheme of epileptic seizures in 1969 (Merlis, 1970, Gastaut, 1970, Dreifuss et al., 1981).
>
> The International League Against Epilepsy further classified partial seizures, separating them into simple and complex, depending on the presence or the impairment of a consciousness state (Dreifuss et al., 1981).
>
> The league also categorized generalised seizures into numerous clinical seizure types, some examples of which are outlined below:...(**Exhibit 1001**, at 2:32-53).

While the '920 patent mischaracterizes the description of the ILAE seizures classification and partial seizures in particular (as the Petitioner will explain in

detail in Part IX. B. of this Petition), it is clear from the passage above that the patentee intended to follow the ILAE classification.

As Professor Marson explains, a key feature of both the 1969 and the 1981 classifications is a distinction between seizures that are generalized from the beginning and those that are partial or focal at onset (i.e. at the beginning) and may become generalized secondary. (**Exhibit 1002**, ¶ 19).

This is also confirmed by scientific literature. For example, McCormick and Contreras, which the '920 patent refers to, states:

'Most epileptic syndromes are grouped in two basic categories: partial and generalized. Partial seizures occur within a localized area of the brain, whereas generalized seizures appear (at least on the level of the electroencephalogram) throughout the forebrain from the outset.' [emphasis added]. (**Exhibit 1008**, pages 815-816).

3. PARTIAL SEIZURES

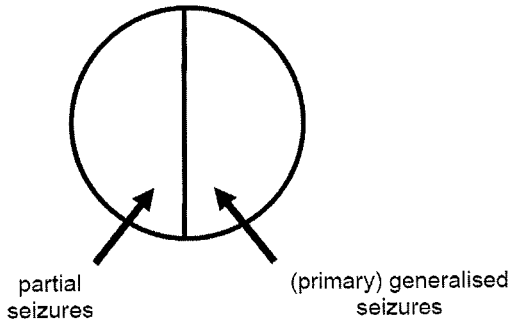
According to the 1981 ILAE classification, partial seizures are divided into three main types: ***simple partial seizures***; ***complex partial seizures***; and ***partial seizures evolving to secondary generalized seizures***. (**Exhibit 1007**, pages 493-494).

During simple partial seizures, consciousness is preserved; the person is alert, can respond to questions or commands, and can remember what occurred during the seizure. (**Exhibit 1002**, ¶ 26).

During complex partial seizures, consciousness is lost; the individual will typically stare and behave automatically. A complex partial seizure may evolve into a secondary generalized seizure (**Exhibit 1002**, ¶ 27).

Partial seizures, whether simple or complex, may progress to secondary generalized seizures. (**Exhibit 1002**, ¶¶ 26-27).

As explained in the Marson Declaration, this can be represented diagrammatically as follows:



(**Exhibit 1002**, ¶ 20).

The key point is that even though partial seizures may evolve into secondary generalized seizures, such seizures are still classified as partial seizures. (**Exhibit 1002**, ¶ 30). This is also confirmed by literature references.

For example, a preeminent expert in the field of epilepsy, Dr. Daniel Lowenstein, states:

> A partial seizure with secondary generalization is often difficult to distinguish from a primary generalized tonic-clonic seizure, since bystanders tend to emphasize the more dramatic, generalized convulsive phase of the seizure and overlook the more subtle, focal symptoms present at onset. In some cases, the focal onset of the seizure becomes apparent only when a careful history identified a preceding aura (i.e., simple partial seizure). Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis. **Nonetheless, distinguishing between these entities is extremely important, as there may be substantial differences in the evaluation and treatment of partial versus generalized seizure disorders.** (**Exhibit 1019**, page 2499, the paragraph bridging the left-hand and the right-hand columns). (Emphasis added).

Thus, as of the effective date of the '920 patent (June 29, 2010), based on the ILAE classification and knowledge in the art, a PHOSITA would interpret the term "partial seizures" in accordance with the 1981 ILAE classification; that is, all seizures which are focal at onset, regardless of whether they later become secondary generalized.

B. CANNABIDIOL (CBD) WAS WELL KNOWN TO TREAT SEIZURES PRIOR TO THE PRIORITY DATE OF THE '920 PATENT

By July 2009, the earliest priority date of the '920 patent, it was well known that CBD could be used to treat seizures. As the '920 patent states, "[t]hree controlled trials have investigated the anti-epilepsy potential of cannabidiol. In each, cannabidiol was given in oral form to sufferers of generalised grand mail (sic) or focal seizures." (**Exhibit 1001**, at 1:58-60).

"Grand mal" seizures are generalized tonic-clonic seizures, the most frequently encountered type of the generalized seizures. (**Exhibit 1007**, page 499, first paragraph in the right hand column).

"Focal seizures" is a synonym for the term "partial seizures." As Dreifuss *et al* explained, when discussing the 1981 ILAE classification:

> "The present proposal does not represent a unanimity of views. There are those who would prefer the substitution of "focal" for "partial" in the description of seizures. The compromise to retain "partial" stems from the compromise arrived at on this very point in the formulation of the 1969 classification." (**Exhibit 1007**, page 490, the paragraph bridging the left-hand and the right-hand columns).

However, by 2006, the ILAE Commission preferred to refer to "focal" rather than "partial" seizures. (**Exhibit 1009**; page 1560, last paragraph in the left-hand column).

Thus, critically, the '920 patent admits that cannabidiol (i.e., CBD) was known for treatment for both generalized and partial seizures.

The '920 patent then describes three studies that describe the use of CBD to treat seizures.

1. CUNHA *ET AL*

First, the '920 patent describes the study by Cunha *et al* (1980). (**Exhibit 1004**). The '920 patent states that Cunha *et al* is a study of 16 grand mal patients. (**Exhibit 1001**, at 1:62-63). This is INCORRECT. Cunha *et al* is a study of 15 patients suffering from "secondary generalized epilepsy with temporal focus". (**Exhibit 1002**, ¶ 49; **Exhibit 1004**, Abstract).

As Professor Marson explains, it is clear from the ILAE classification and from the explanatory tables in Dreifuss *et al* (**Exhibit 1007**, pages 493-495) that the 15 patients suffering from "secondary generalized epilepsy with temporal focus" had partial seizures. (**Exhibit 1002**, ¶ 50).

First, he states that these seizures had a focal onset, arising from a temporal lobe as evidenced by the phrase "with temporal focus." (**Exhibit 1002**, ¶ 51).

Second, Professor Marson states that Cunha *et al* state that there was electroencephalogram (EEG) evidence to support a diagnosis of temporal lobe

epilepsy. (**Exhibit 1002**, ¶ 52). Temporal lobe epilepsy means that the patients had partial seizures.

Third, Professor Marson states that because of the first and second points, it is inconceivable that the patients included in the trial were experiencing **both** secondary generalized seizures and primary generalized seizures. (**Exhibit 1002**, ¶ 53). Therefore, the only generalized seizures they were experiencing must have been secondary generalized seizures, which are partial seizures.

Fourth, the statement in Table 1 on page 179 of Cunha *et al* that "All of the eight patients in the CBD group have counts of greater than zero in the 'focal convulsive crises' column in at least one of two baseline weeks," **means that all patients had simple and/or complex partial seizures** during baseline. (**Exhibit 1002**, ¶ 54).

Fifth, Cunha *et al* state in Table 3 on page 180 that "This table summarizes the EEG abnormalities at baseline and during follow up. The data collected at baseline are for temporal lobe abnormalities, either left, right, or bilateral." As Professor Marson explains, the focus on temporal lobe abnormalities confirms that patients had a temporal lobe focus, and therefore, the patients were believed to have temporal lobe epilepsy, which manifests with partial seizures and secondary generalized seizures. (**Exhibit 1002**, ¶ 55).

Cunha *et al* report that all patients received their regular medication and 200-300 mg of either CBD or a placebo. (**Exhibit 1004**, Abstract). Of the eight patients who received CBD, 4 demonstrated almost complete improvement, 3 demonstrated partial improvement, and 1 remained unchanged. (**Exhibit 1004**, Abstract). In contrast, of the other eight patients who received a placebo (one patient was both a placebo patient and then a CBD patient), only one patient improved, while seven had no improvement. Cunha *et al* also report that all patients tolerated CBD very well and no toxicity or serious side effects were detected. (**Exhibit 1004**, Abstract).

Accordingly, Cunha *et al* disclose: 1) the use of CBD to treat partial seizures; 2) administration of 200-300 mg of CBD daily; 3) no toxicity or serious side effects; and 4) the treatment was mostly effective.

2. AMES *ET AL*

The '920 patent then describes a study by Ames *et al* (1986) whereby 12 institutionalized patients who had frequent seizures were given either a placebo or 200-300 mg of CBD per day. (**Exhibit 1011**). While the study did not find a statistically significant difference in seizure frequency, Ames *et al* state that the study was cut short for independent reasons. However, their plan was to increase the CBD dosage because they suspected that CBD's lack of efficacy might have

been due to the fact that the patients were brain-damaged and severely epileptic. (**Exhibit 1011**).

Professor Marson states that in view of Ames *et al*, a PHOSITA would have concluded that further studies of CBD, testing a range of doses with rigorous design, are required. (**Exhibit 1002**, ¶ 60).

Accordingly, Ames *et al* disclose the use of 200-300 mg of CBD daily to treat seizures and suggest increasing the amount of CBD to treat seizures.

3. BHATTACHARYYA *ET AL*

Bhattacharyya *et al* report that CBD is safe at doses of 600 mg per day when administered to humans. (**Exhibit 1012**, Abstract at page 442).

As Professor Marson explains, Bhattacharyya *et al* set out to investigate the effects of Δ9-tetrahydrocannabinol (Δ9-THC) and CBD on regional brain function during verbal learning. (**Exhibit 1002**, ¶ 58). When ingested at a dose of 600 mg per day, CBD did not have any negative effect on the patients, such as increase psychotic symptoms, levels of anxiety, intoxication and sedation (**Exhibit 1012**, Abstract, page 445; and **Exhibit 1002**, ¶ 58). The authors stated that this finding is consistent with evidence that CBD does not affect learning and memory. (**Exhibit 1012**, page 445; and **Exhibit 1002**, ¶ 58).

To summarize, the prior art teachings contained in the '920 patent clearly disclose that: a) CBD was known to treat seizures; b) CBD was known to treat

partial seizures and, in particular, secondary generalized seizures; c) CBD was effective in treating seizures, including partial seizures; d) doses of 600 mg of CBD were administered to humans without any toxicity or serious side effects.

IX. CLAIM CONSTRUCTION

In *inter partes* review, a claim term must be given its "broadest reasonable construction in light of the specification," See, 37 C.F.R. §42.100(b); see also *In re Cuozzo Speed Techs.,* 793 F.3d 1268, 1279 (Fed. Cir. 2015). Thus, the broadest reasonable interpretation (BRI) standard must be applied.

Terms not explicitly discussed below should be construed to have their plain and ordinary meanings consistent with the specification.

Critically, this Petition centers around the definition of the term "partial seizures."

A. Broadest Reasonable Interpretation of "Partial Seizures"

The broadest reasonable interpretation of the term "partial seizure" is a definition in accordance with the 1981 ILAE seizure classification; that is *a seizure which originated in a specific brain region, which can be simple or complex, and which may remain localized or become secondarily generalized, i.e. become a secondary generalized seizure.*

B. The Patentee's Statements With Respect to "Partial Seizures" Are Misleading and Inconsistent with the Cited References and the ILAE Classification

The patentee stated that "partial seizures originate in specific brain regions and remain localized--most commonly the temporal lobes (containing the hippocampus), whereas generalized seizures appear in the entire forebrain as a secondary generalization of a partial seizure (McCormick and Contreras, 2001, Lutz 2004)," (**Exhibit 1001**; at 2:36-41). This statement is inaccurate, inconsistent with the very references cited by the patentee, and misleading because it creates the false impression that this incorrect and unusual definition is endorsed by the cited references, McCormick and Contreras, 2001, Lutz 2004. (**Exhibit 1002**, ¶¶ 35-46).

In the very next sentence, the patentee states that: "[t]his concept of partial and generalized seizure classification did not become common practice until the International League Against Epilepsy published a classification scheme of epileptic seizures in 1969 (Merlis, 1970, Gastaut, 1970, Dreifuss *et al.*, 1981). (**Exhibit 1001**; at 2:41-46). This statement is even more misleading because it implies that the patentee's definition of the term "partial seizures" is in accordance with the ILAE classification. It is not.

As Professor Marson explains, a key feature of the ILAE classification is a distinction between seizures that are generalized from the beginning and those that are partial or focal at onset (i.e. at the beginning) and may become generalized secondary. (**Exhibit 1002**, ¶ 19).

Contrary to the patentee's statement, neither McCormick and Contreras nor Lutz ever state that partial seizures remain localized. (**Exhibit 1002**, ¶¶ 36-40). On the contrary, McCormick and Contreras state that generalized seizures appear (at least on the level of the electroencephalogram) throughout the forebrain **from the outset** (emphasis added). (**Exhibit 1002**, at ¶ 22). Here is the direct quote from McCormick and Contreras:

> 'Most epileptic syndromes are grouped in two basic categories: partial and generalized. Partial seizures occur within a localized area of the brain, whereas generalized seizures appear (at least on the level of the electroencephalogram) throughout the forebrain from the outset.' [emphasis added]. (**Exhibit 1008**, pages 815-816).

There is nothing in Lutz to contradict this definition, as Lutz merely refers back to McCormick and Contreras. (**Exhibit 1002**, at ¶ 39).

With respect to generalized seizures, Dreiffus *et al*, describing the 1981 ILAE classification, state that "[g]eneralized seizures are those in which the first

clinical changes indicate initial involvement of both hemispheres. (**Exhibit 1007**, page 494).

The patentee's statement that "[g]eneralised seizures appear in the entire forebrain as a secondary generalisation of a partial seizure" is also incorrect. On the contrary, generalized seizures do not appear in the entire forebrain as a secondary generalization of a partial seizure, but rather are generalized from the outset. (**Exhibit 1002**, at ¶ 29). Generalized seizures and secondary generalized seizures are two very different types of seizures. Therefore, it is incorrect to say that generalized seizures appear as a secondary generalization of a partial seizures. As Professor Marson explains, there is a clear distinction between seizures that are generalized from the beginning and those that are partial or focal at onset and become generalized secondary. This distinction is clinically significant. (**Exhibit 1002**, at ¶¶ 19 and 23).

The '920 patent goes on to say, "The International League Against Epilepsy further classified partial seizures, separating them into simple and complex, depending on the presence or the impairment of a consciousness state (Dreifuss *et al.*, 1981)." Again, this is misleading as this definition omits those partial seizures – simple or complex – which evolve to secondary generalized seizures.

As Professor Marson explains, Dreifuss classifies these partial seizures into Group C - partial seizures evolving to generalized tonic clonic convulsions. (**Exhibit 1002**, ¶ 45); (**Exhibit 1007**, page 493-494).

Another expert in this field, Dr. Lowenstein, likewise explains that partial seizures with secondary generalization fall within the group of "partial seizures" and that it is important to distinguish primary generalized seizures from secondary generalized seizures. (**Exhibit 1019**, Table 363-1 on page 2498, and page 2499, the paragraph bridging the left-hand and the right-hand columns).

Accordingly, the ILAE classification is clear in defining partial seizures into three main types: simple partial seizures; complex partial seizures; and partial seizures evolving to secondary generalized seizures. (**Exhibit 1007**, pages 493-494). Therefore, the patentee's statement that partial seizures remain localized is unusual, incorrect, and inconsistent with the 1981 ILAE classification, the accepted standard in the field of epilepsy.

C. The Patentee Did Not Define the Term "Partial Seizure" With Any Clarity, Deliberateness or Precision and Did Not Give One of Ordinary Skill in the Art Notice of the Change in Meaning

While the patentee can act as a lexicographer, the Federal Circuit made it clear that if the patentee's definition varies from the normal definition, the patentee must define the terms "with reasonable clarity, deliberateness, and precision" and,

if done, must "set out his uncommon definition in some manner within the patent disclosure" so as to give one of ordinary skill in the art notice of the change" in meaning. *See*, *In re Paulsen,* 30 F.3d 1475, 1480 (Fed. Cir. 1994), citing *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387-88 (Fed. Cir. 1992).

Here, there can be no question that the patentee did not define the term "partial seizure" with "reasonable clarity, deliberateness, and precision" required by the Federal Circuit. On the contrary, the patentee created a misleading impression that its unusual definition of the term "partial seizures" is in agreement with the cited references and the 1981 ILAE, which is a gold standard for seizure classifications. Because of this misleading impression, one of ordinary skill in the art had no notice of the change in meaning of this term. This directly contradicts the Federal Circuit's mandate that the uncommon definition must be set out so as to give notice of the change in meaning.

A PHOSITA who reads the specification of the '920 patent would be very confused. On the one hand, the patentee sets out an unusual definition of the term "partial seizures", which is inconsistent with the industry definition and the very references cited by the patentee as allegedly supporting its definition; and on the other hand, the patentee strongly implies that its definition is in accordance with the ILAE classification. As Professor Marson stated, the definition of the term "partial seizure" in the '902 patent is either a typing or clerical error, or a

misunderstanding of the ILAE classification and the cited references. (**Exhibit 1002**, ¶ 46).

Therefore, given: a) the requirement that that claim term be given a broadest reasonable interpretation; b) unambiguous teachings of McCormick and Contreras, Dreifuss *et al*, Lowenstein, and the ILAE classification; c) the patentee's lack of any explanation or notice that its definition differs from the accepted definition; and d) the patentee's lack of any reasonable clarity, deliberateness and precision, the term "partial seizure" should be construed as a seizure which originated in a specific brain region, which can be simple or complex, and which may remain localized or become secondarily generalized, i.e. become a secondary generalized seizure.

X. THE '920 PATENT IS NOT ENTITLED TO JULY 3, 2009 PRIORITY DATE AND MUST RELY ONLY ON ITS FILING DATE OF JUNE 29, 2010.

None of the claims of the '920 patent are entitled to the priority date of the foreign application number GB 0911580.9 filed July 3, 2009 and to which the '920 patent claims priority.

The statute provides that priority may only be claimed to a patent application directed to "the same invention." *See*, 35 U.S.C. §119(a):

> (a) An application for patent for an invention filed in this country by any person who has, or whose legal representatives or assigns have,

> previously regularly filed an application for a patent **for the same invention** in a foreign country which affords similar privileges in the case of applications filed in the United States or to citizens of the United States, or in a WTO member country, shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country, if the application in this country is filed within 12 months from the earliest date on which such foreign application was filed. 35 U.S.C. §119(a).

In the context of US-filed priority applications, the courts have held that the disclosure of the invention in the prior application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. §112(a) except for the best mode requirement. *See, Transco Prods., Inc. v. Performance Contracting, Inc.,* 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The same logic must be applied to foreign-filed priority applications.

Accordingly, the disclosure of the prior-filed application must provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. §112(a) except for the best mode requirement.

There can be no question that the disclosure of the foreign application number GB 0911580.9 (**Exhibit 1013**) is not directed to the "same invention" and does not comply with the requirements of 35 U.S.C. §112(a).

The invention of the '920 patent, as embodied by the claims, is directed to a method of treating **partial seizure** comprising administering cannabidiol (CBD) to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg. (**Exhibit 1001**, at 15:5-8). The priority application does not mention even once the term "**partial seizure**." For example, in paragraph [0001], it states that "[t]his invention relates to the use of one or more cannabinoids in the treatment of epilepsy and more particularly to the use of one or a combination of cannabinoids in the treatment of **generalized seizure**." (**Exhibit 1013**, paragraph [0001] at page 1). None of the claims of the priority application mention partial seizure. Instead, all claims are directed to the treatment of generalized seizures. (**Exhibit 1013**, pages 16-17).

Further, in contrast with the '920 patent, the priority application does not contain any Figure corresponding to Figure 20 of the '920 patent which describes the effect of CBD on penicillin induced seizure severity and mortality. This penicillin-induced seizures model, as the '920 patent itself explains, is the model for partial seizures. (**Exhibit 1001**, 12:34-37).

Further, while the '920 patent has six Examples, including Example 6 which concerns the effects of pure CBD in penicillin induced seizures, the priority application has only three Examples, each relating to the pentylenetetrazole (PTZ)-induced model. As the '920 patent itself explains, the PTZ model is the model of generalized seizures. (**Exhibit 1001**, 5:64-67).

To summarize, the priority application is not directed to the same invention as the invention of the '920 patent. The priority application does not mention "partial seizures" anywhere in its disclosure and does not contain any disclosure which could even conceivably provide any support for the invention of the '920 patent.

Therefore, the '920 patent is not entitled to the priority date of July 3, 2009 and can only rely on its own filing date of June 29, 2010 as the effective filing date.

XI. PROSECUTION HISTORY OF THE '920 PATENT

A. Prosecution History and Reasons for Allowance

The application that issued as the '920 patent (application no. 13/380,305) was filed as the International Patent Cooperation Treaty (PCT) Application on June 29, 2010. (**Exhibit 1001**; cover page). This PCT application entered the U.S. National Stage on March 9, 2012. (**Exhibit 1001**; cover page). Applicants filed three Preliminary Amendments on December 22, 2011, March 19, 2012 and May

23, 2014. (**Exhibit 1005**, page 2). All of the ultimately issued claims were introduced in their final form by the Third Preliminary Amendment filed on May 23, 2014. (**Exhibit 1014**, pages 2-3).

In the Office Action dated August 25, 2014, the Examiner indicated that all of the ultimately issued claims are allowable over the prior art. The Examiner stated that:

> While the prior art was aware that CBD with or without THCV provided an effective treatment for epilepsy, the reference WO 02/064109, (cited by Applicants), is believed to teach away from the presently claimed subject matter because at the paragraph bridging pages 4-5, a dosage of "at least 400 mg." of a cannabinoid, which includes CBD and/or THCV, (see page 27 at lines 30-31), is effectively taught as problematic. In particular, daily dosages of up to 120 mg. of a cannabinoid are taught as being a problem to overcome. i.e. by delivering less dosages of a cannabinoid.
>
> In light of the above, it is not seen that the prior art would anticipate or make obvious the subject matter of claims 10, 15 and 18-28....
>
> (**Exhibit 1005**, pages 2-3).

Following this Office Action, Applicants promptly canceled two claims rejected by the Examiner (not at issue here), and the application was formally allowed on December 10, 2014. (**Exhibit 1015**).

B. The Examiner Misunderstood the Key Reference WO 02/064109

As the above-quoted text of the Office Action mailed on August 25, 2014 makes clear, the Examiner allowed this application based on the belief that WO 02/064109 (WO '109) teaches away from the present invention. The Examiner explicitly admitted that the prior art "was aware that CBD with or without THCV provided an effective treatment for epilepsy" but stated that "the reference WO 02/064109, (cited by Applicants), is believed to teach away from the presently claimed subject matter." (**Exhibit 1005**, page 2, last paragraph). This belief was based on a fundamental misunderstanding of WO '109.

Contrary to the Examiner's belief, WO '109 does not teach away from the claimed invention, and actually suggests using CBD at high daily dosages.

The Federal Circuit explained that "[a] reference "teaches away" when it "suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by applicant." *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (internal citations omitted). In other words, a reference "teaches away" when a PHOSITA "would be led in a direction divergent from the path that was taken by the applicant." *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008).

The Examiner stated that WO '109 teaches away from the claimed invention because a dosage of "at least 400 mg" of a cannabinoid is "effectively taught as

problematic" at the paragraph bridging pages 4 and 5 of WO '109. (**Exhibit 1005**, page 2). According to the Examiner, "daily dosages of up to 120 mg. of a cannabinoid are taught as being a problem to overcome. i.e. by delivering less dosages of a cannabinoid." (**Exhibit 1005**, pages 2-3).

The relevant paragraph of WO '109 is as follows:

> The preparation of liquid formulations for oropharangeal delivery of cannabinoids poses a number of problems. First, it is necessary to deliver at least 1.0 mg, more preferably at least 2.5mg and even more preferably at least 5mg of cannabinoids per 0.1ml of liquid formulation to achieve a therapeutic effect in a unit dose. In this regard a patient may require up to 120mg cannabinoid/day, on average around 40mg/day to be taken in a maximum of six doses. (**Exhibit 1006**, pages 4-5).

This language does not state or imply that one should not use dosages above 120 mg cannabinoid per day, or that such dosages would be ineffective, or that lower dosages should be used instead. Rather, WO '109 was explaining the challenges of preparing liquid formulations of cannabinoids when relatively high amounts of cannabinoids needed to be dissolved.

As Professor Benet explains, WO '109 is directed to overcoming the problem that cannabinoids undergo the so-called "first pass effect", wherein more than 90% of an ingested dose is metabolized when first administered to a patient.

(**Exhibit 1003**, ¶ 41). The solution that WO '109 proposes is to formulate CBD in such a way so that it avoids first pass metabolism and is absorbed directly into the bloodstream. (**Exhibit 1003**, ¶ 42).

WO '109 explains that in the case of a sublingual or buccal delivery, at least 1 mg of cannabinoids per 0.1 ml of liquid formulation needs to be delivered to a patient in an amount of formulation which will not be swallowed by the patient. (**Exhibit 1006**, page 5, lines 7-12).

Therefore, larger doses of cannabinoids needed to be formulated and solubilized. Then, WO' 109 goes on to explain the specific problem and the proposed solution:

> Whilst such amounts can be achieved by dissolving the cannabinoid in ethanol as the solvent, high concentrations of ethanol provoke a stinging sensation and are beyond the limit of tolerability.
>
> There is thus a need to use a co-solvent in order to reduce the amount of ethanol, whilst still enabling sufficient quantities of cannabinoid to be solubilised.
>
> The applicant has discovered that the choice of co-solvent is limited and should be selected from either:..." (**Exhibit 1006**, page 5, lines 14-26).

Thus, WO '109 does not suggest using lower doses of cannabinoids. On the contrary, it teaches how to better solubilize the required high doses of

cannabinoids. WO '109 is not concerned with specific diseases or dosages required to treat any diseases or conditions. The reference as a whole is directed to preparation of pharmaceutical formulations. (**Exhibit 1006**, Abstract, Examples, Claims).

Moreover, WO '109 suggests using **higher** dosages of cannabinoids because it explains that cannabinoids are poorly absorbed due to a "first pass" metabolism, whereby the liver removes up to 90% of an ingested dose. (**Exhibit 1006**, page 1, lines 20-25). Because the challenged claims of the '920 patent do not exclude any routes of administration of CBD, WO '109 actually helps to render the '920 patent obvious since it suggests higher oral doses of CBD to counteract the first pass effect. (**Exhibit 1003**, ¶ 45).

The reference does not teach any specific dosages of cannabinoids as "problematic"; does not state or imply that dosages should not exceed 120 mg cannabinoid per day; does not report any side effects or toxicities associated with using more than 120 mg cannabinoid per day; and is not concerned with specific dosages *per se.*

Therefore, a PHOSITA familiar with the disclosure of WO '109 would not have concluded that one should avoid using more than 120 mg cannabinoid per day. Instead, the PHOSITA would have recognized that WO '109 teaches how to better solubilize cannabinoids. The PHOSITA would have concluded that when

liquid formulations of cannabinoids are desired, one could follow one of the proposed solutions of WO '109, such as using a co-solvent taught by this reference.

Accordingly, the Examiner's conclusion that WO '109 teaches away from the invention was completely inconsistent with the teachings of WO '109. (**Exhibit 1003**, ¶ 46).

Even if it was true (and it is not) that WO '109 taught daily dosages of up to 120 mg cannabinoid as problematic, the reference would still not have taught away from the invention because it would not have led a PHOSITA in a direction divergent from the path that was taken by the patentee of the '920 patent. There is nothing in the reference to suggest that using 120 mg or more (such as at least 400 mg) of cannabinoid per day is unlikely to be successful. On the contrary, the reference teaches how to successfully deliver high amounts of cannabinoid to patients.

XII. THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER THE PRIOR ART

A. Identification of the Challenge (37 C.F.R. §42.104(b))

Insys requests *inter partes* review of each claim of the '920 patent based on Section 103 obviousness based on the references listed in the index below. The references include those that were examined by the PTO and those not previously

considered by the PTO but consistent and supplemental to those references. Per 37 C.F.R. §42.6(d), copies of the references are filed herewith.

Cunha *et al*, Jones *et al*, Ames *et al*, and WO 2009/007697 were disclosed to the USPTO during the prosecution of the '920 patent. Moreover, the Examiner acknowledged that "the prior art was aware that CBD with or without THCV provided an effective treatment for epilepsy" but explained that he believed that another reference, WO '109, teaches away from the invention by allegedly teaching that dosages of at least 400 mg of a cannabinoid were "problematic." (**Exhibit 1005**, pages 2-3). As Insys has explained in the Section XI. B of this Petition, this belief was absolutely incorrect as WO '109 teaches no such thing. Therefore, the Examiner would not have allowed the claims but for his mistaken belief that WO '109 teaches away from the invention.

The Petitioner believes that its interpretation of Cunha *et al*, Jones *et al*, Ames *et al*, and WO 2009/007697 is consistent with the Examiner's interpretation of these references.

Ground	**35 U.S.C. Section (pre-3/16/2013)**	**Index of References**	**'920 Patent Claims**
I	§103	Cunha *et al* in view of Bhattacharyya *et al*, Ames *et al*, Lowenstein and WO 2009/007697	1-13

II	§103	Cunha *et al* in view of Pertwee *et al*, Malfait *et al*, Lindamood *et al*, Mechoulam *et al*, Zuardi *et al*, and WO 2009/007697	1-13
III	§103	Jones *et al* in view of Cunha *et al*, Lowenstein and WO 2009/007697	1-13

B. Ground I: Independent Claim 1 and Dependent Claims 2-13 Are Obvious Under §103(a) Over Cunha *et al* in View of Bhattacharyya *et al*, Ames *et al*, Lowenstein and WO 2009/007697

1. Availability of References As Prior Art

Cunha *et al* and Ames *et al* have been disclosed in the prosecution of the '920 patent. Bhattacharyya *et al* and Lowenstein are new references consistent with Cunha *et al* and Ames *et al*. These references are available as prior art against the '920 patent as follows.

The effective filing date of the '920 patent is June 29, 2010 (its filing date). As the Petitioner has demonstrated in Section X of this Petition, the '920 patent is not entitled to the priority date of July 3, 2009.

Cunha *et al* is a scientific article which was published in the journal Pharmacology in 1980. (**Exhibit 1004**). It is also discussed in the Background

section of the '920 patent. (**Exhibit 1001**, at 1:62 through 2:2). Accordingly, Cunha *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA) and also as Applicant's Admitted Prior Art.

Bhattacharyya *et al* is a scientific article which was published in the Journal of Archives General Psychiatry in April, 2009 (e-publication). (**Exhibit 1012**). Accordingly, Bhattacharyya *et al* is available as prior art under at least 35 U.S.C. §102(a) (pre-AIA).

Ames *et al* is a publication in the South African Medical Journal 69:14 (1986). (**Exhibit 1011**). It is also discussed in the Background section of the '920 patent. (**Exhibit 1001**, at 2:3-6). Accordingly, Ames *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA) and also as Applicant's Admitted Prior Art.

Lowenstein is chapter 363 from the book entitled *Seizures and Epilepsy*, co-authored by Fauci AS, Kasper DL, Longo DL, eds. Harrison's Principles of Internal Medicine, 17th ed. Section 2: Diseases of the Central Nervous System. New York: McGraw-Hill (2008). The book was published in 2008. Accordingly, Lowenstein is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

WO '697 is an International Patent Application Publication published on January 15, 2009. (**Exhibit 1020**, cover page). Accordingly, WO '697 is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

2. Independent Claim 1

Claim 1 is directed to a method of treatment of partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

The prior art teaches or suggests all elements of this claim.

Cunha *et al* Teaches Treatment of the Same Disease with the Same Drug

Cunha *et al* is a study of 15 patients suffering from "secondary generalized epilepsy with temporal focus". (**Exhibit 1004**, Abstract).

As Professor Marson explains, it is clear from the ILAE classification and from the explanatory tables in Dreifuss *et al* (**Exhibit 1007**, pages 493-495) that the 15 patients suffering from "secondary generalized epilepsy with temporal focus" are classified as patients having partial seizures. (**Exhibit 1002**, ¶ 50). These seizures had a focal onset as evidenced by the phrase "secondary generalized epilepsy with temporal focus" and therefore, under the ILAE classification, these patients must be classified as suffering from partial seizure.

As explained in Section VIII.A.3 of this Petition, "partial seizures" consist primarily of three main types: 1) simple partial seizures; 2) complex partial seizures; and 3) partial seizures evolving to secondary generalized seizures. Thus, Cunha *et al* disclose the treatment of a species of the genus of "partial seizures"

(wherein the "partial seizures evolving to secondary generalized seizures" is the species).

Despite the Patentee's attempt to re-define the "partial seizure" as a seizure that originates in specific brain regions and remains localized, the term "partial seizure" must be construed consistently with the ILAE definition, as a seizure that originates in specific brain regions, whether or not it remains localized. As Insys has explained in Section IX of this Petition:

1) The ILAE classification clearly distinguishes between seizures that are generalized from the beginning and those that are partial or focal at onset (i.e. at the beginning) and may become generalized secondary. (**Exhibit 1002**, ¶ 19).

2) Contrary to the patentee's statement, neither McCormick and Contreras nor Lutz (the references that allegedly stated that partial seizures remain localized) ever state that partial seizures remain localized. (**Exhibit 1002**, ¶¶ 36-40).

3) Dr. Lowenstein explains that partial seizures with secondary generalization fall within the group of "partial seizures" and that it is important to distinguish primary generalized seizures from secondary generalized seizures. (**Exhibit 1019**, Table 363-1 on page 2498, and page 2499, the paragraph bridging the left-hand and the right-hand columns).

4) The Patentee did not give any notice or explanation that its definition of the term "partial seizures" differs from the widely accepted definition, and in fact created the incorrect impression that its definition is the same as the ILAE definition.

Thus, under the proper claim construction of the term "partial seizure," Cunha *et al* disclose the use of the same drug (CBD) to treat the same disease (partial seizure) as the method recited in claim 1.

Accordingly, the only difference between the disclosure of Cunha *et al* and the method recited in claim 1 of the '920 patent is the recited daily dosage of at least 400 mg.

The Claimed Daily Dosage of At Least 400 mg CBD Is Predictable, Safe and Expected In View of Cunha *et al*, Bhattacharyya *et al*, and Ames *et al*

The identification of the claimed dosage of at least 400 mg is nothing more than "the optimization of a range or other variable within the claims that flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer, Inc. v. Apotex*, 480 F.3d 1348, 1369 (Fed. Cir. 2007) citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

Cunha *et al* teach that:

"[i]n phase 1, 3-6 mg/kg of CBD (roughly corresponding to 200-400 mg/subject) was administered daily to healthy human volunteers for 30 days. In phase 2, patients suffering from secondary generalized epilepsy with temporal irritative activity received 200-300 mg of the drug for periods of up to 4.5 months." (**Exhibit 1004**, page 177, top left-hand column).

Throughout the reference, Cunha *et al* repeatedly state that these dosages were well tolerated and no toxicity or serious side effects were observed.

All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. (**Exhibit 1004**, Abstract).

There is hardly any toxicity as shown in our phase 1 study. (**Exhibit 1004**, page 182, second paragraph in the right-hand column).

A similar absence of toxicity was also noted in our phase 2 study in which 8 epileptic patients received 200 or 300 mg for up to 41/2 months. Furthermore, none of the 16 subjects receiving CBD showed any psychic Δ1-THC-type effects. (**Exhibit 1004**, page 182, second paragraph in the right-hand column).

Somnolence reported by 3 healthy volunteers and 4 epileptic patients (43% of the subjects receiving the drug) was the only CBD side effect noted. (**Exhibit 1004**, page 182, third paragraph in the right-hand column).

Cunha *et al* explicitly disclose that CBD was administered at dosages "roughly corresponding to 200-400 mg/subject" to healthy volunteers without any serious side effects or toxicities. (**Exhibit 1004**, page 177). It is undisputed that the claimed amount "which provides a daily dose of at least 400 mg" falls within the range disclosed in Cunha *et al*.

Cunha *et al* further report that of the eight patients who received CBD, at dosages of 200-300 mg per day, four patients demonstrated almost complete improvement, three demonstrated partial improvement, and one remained unchanged. (**Exhibit 1004**, Abstract). In contrast, out of the eight patients who received a placebo (one patient was both a placebo patient and then a CBD patient), only one patient improved, while seven had no improvement.

Bhattacharyya *et al* also teach that CBD is extremely well tolerated in humans and that CBD doses of 600 mg do not result in any psychotic or other negative symptoms.

Specifically, CBD at doses of 600 mg does not have any negative effects on the patients associated with Δ9-THC. (**Exhibit 1012**, page 445, middle of right-hand column; **Exhibit 1002**, ¶ 57).

Thus, Cunha *et al* and Bhattacharyya *et al* both establish that CBD was very well tolerated in humans.

Ames *et al* report a study of 12 epileptic patients who had frequent seizures and who were given 200-300 mg CBD per day. (**Exhibit 1011**). While the study did not find a statistically significant difference in seizure frequency, and had to be cut short for independent reasons, Ames *et al* planned to increase the CBD dosage because they suspected that CBD's lack of efficacy might have been due to the fact that the patients were brain-damaged and severely epileptic. (**Exhibit 1011**).

Accordingly, Ames *et al* suggest increasing the daily amount of CBD from 200-300 mg to treat seizures.

Therefore, a PHOSITA familiar with the disclosures of Cunha *et al*, Bhattacharyya *et al*, and Ames *et al* would have understood that CBD administered at 200-300 mg per day was generally effective, although in some patients the improvement was partial. As Professor Marson states, a PHOSITA would have understood that there was a reasonable likelihood that CBD administered at 200-300 mg per day might have efficacy as a treatment for partial seizures, and would have also believed that the amount of CBD administered to a patient could be safely increased to arrive at the optimal dosage. (**Exhibit 1002**, ¶ 64).

Accordingly, it would have been obvious for a PHOSITA to optimize the daily dosages of CBD by increasing them to at least 400 mg per day in order to increase the effectiveness of the drug. Thus, to arrive at the daily dosage of at least

400 mg of CBD for the treatment of partial seizures was well within a skill in the art and obvious.

Secondary Considerations Do Not Overcome the *Prima Facie* Case of Obviousness

Any evidence of secondary considerations, if presented by GW Pharma and Otsuka, will not overcome the strong *prima facie* case of obviousness set forth in this Petition.

First, the evidence of obviousness is so strong (CBD was shown to successfully treat partial seizures at 300 mg daily; prior art suggested increasing the dosage; and CBD was shown to be safe and well tolerated at much higher dosages) that no evidence of secondary considerations can overcome it. The Federal Circuit has repeatedly held that if a prima facie case of obviousness is strong, secondary considerations will not be enough to demonstrate non-obviousness. See, for example, *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011) ("A strong case of prima facie obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1306 (Fed. Cir.

2010) (concluding the objective evidence of nonobviousness would "fail to make a difference" in light of strong evidence of obviousness).

Second, even if secondary considerations of obviousness are considered (for example, long-felt need, industry skepticism, etc), there are compelling logical explanations that have nothing to do with the obviousness. For example, the gap between publication of Cunha *et al* (1980) and the filing date of the '920 patent (2010) is easily explained by reasons that have nothing to do with the obviousness of the invention. As Cortesi *et al* explain in 2006:

> "although the anticonvulsive properties of CBD have been known since the early eighties [2], only a few recent papers have addressed its use in samples affected with epileptic disorders. The major reasons for the lack of clinical research have been the introductions of new synthetic and more stable pharmaceutical anticonvulsants, the recognition of important adverse effects and the legal restriction to the use of cannabis-derived medicines [1]."
>
> (**Exhibit 1029**, page 920, internal citations omitted).

Further to this point, medicinal marijuana was not legal in the United States until the 1990s-2000s: California in 1996, Alaska in 1998, Colorado in 2000, many other states in recent elections. Recreational use became legal even more recent. Therefore, there was little reason for pharmaceutical companies to conduct clinical research for CBD.

Accordingly, the gap between the publication of Cunha *et al* and the filing date of the '920 patent does not support the non-obviousness of the invention claimed in the '920 patent.

Prior Art Does Not Teach Away from the Invention

As to "teaching away," while the Examiner cited WO 02/064109 as allegedly teaching away from the invention, this reference does not in any way teach away from the invention, much less from the full scope of claim 1, for the reasons explained in Section XI.B of this Petition. Specifically, the reference does not teach any specific dosages of cannabinoids as "problematic"; does not state or imply that dosages should not exceed 120 mg cannabinoid per day; does not state or imply that dosages exceeding 120 mg cannabinoid per day would not be successful; does not report any side effects or toxicities associated with using more than 120 mg cannabinoid per day; and is not concerned with specific dosages *per se.* Instead, the reference teaches how to deal with solubility challenges of cannabinoids. It also suggests increasing the dosage of cannabinoids by disclosing the first pass effect resulting in more than 90% of ingested CBD being metabolized. (**Exhibit 1003**, ¶ 13). A PHOSITA familiar with the disclosure of WO '109 would not have concluded that one should avoid using more than 120 mg cannabinoid per day. On the contrary, a PHOSITA would have concluded that the dosage should be increased to compensate for the first pass effect. (**Exhibit 1003**,

¶ 45). Accordingly, the Examiner's conclusion that WO '109 teaches away from the invention was completely inconsistent with the teachings of WO '109.

Regardless of How the Term "Partial Seizure" is Construed, Claim 1 Is Still Obvious Over Cunha *et al* in View of Bhattacharyya *et al*, Ames *et al* and Lowenstein

Even if the term "partial seizure" is construed to only cover partial seizures contrary to the ILAE classification and well-accepted understanding of this term, claim 1 would still be obvious over Cunha *et al* in view of Bhattacharyya *et al*, Ames *et al*, and Lowenstein because CBD was effective for the treatment of generalized seizures and that would make it obvious to use CBD to treat partial seizures.

As explained above, Cunha *et al* teach the treatment of secondary generalized seizures with 200-300 mg daily dosages of CBD. Cunha *et al* and Bhattacharyya *et al* also teach that the CBD was effective to treat secondary generalized seizures and had a safe profile with no significant side effects. Ames *et al* explicitly suggest increasing the daily dose of CBD to treat seizures.

Lowenstein teaches that there is a large overlap between the drugs which are used to treat partial seizures and the drugs that are used to treat generalized seizures. (**Exhibit 1019**, pages 2507-2509).

> Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. However, there is considerable overlap between many antiepileptic drugs, such that the choice of therapy is often determined more by the patient's specific needs, especially his/her assessment of side effects. (**Exhibit 1019**, page 2507, fourth paragraph in the right-hand column). (Emphasis added).

Specifically, the drugs such as carbamazepine (or oxcarbazepine), phenytoin, lamotrigine, and topiramate are all approved for the initial treatment of partial seizures, including secondary generalize. (**Exhibit 1019**, page 2507). Lowenstein also states that valproic acid is also an effective alternative for some patients with partial seizures, especially when the seizures secondary generalize. (**Exhibit 1019**, page 2509, first full paragraph). Lowenstein then lists valproic acid, lamotrigine (the best initial choices), phenytoin, topiramate, carbamazepine and zonisamide as suitable for the treatment of generalized seizures. (**Exhibit 1019**, page 2509, third full paragraph).

As one can see, there is a very large overlap between the drugs suitable for treatment of partial seizures and the drugs suitable for treatment of generalized seizures.

This is further supported by the fact that many of the mechanisms by which antiepileptic drugs work would be expected to treat both partial and generalized seizures. Lowenstein explains that:

> [a]ntiepileptic drugs appear to act primarily by blocking the initiation or spread of seizures. This occurs through a variety of mechanisms that modify the activity of ion channels or neurotransmitters, and in most cases the drugs have pleiotropic effects. The mechanisms include inhibition of Na^+-dependent action potentials in a frequency-dependent manner (e.g., phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide), inhibition of voltage-gated Ca^{2+} channels (phenytoin), decrease of glutamate release (lamotrigine), potentiation of GABA receptor function (benzodiazepines and baribiturates), increase in the availability of GABA (valproic acid, gabapentin, tiagabine), and modulation of release of synaptic vesicles (levitiracetam). (**Exhibit 1019**, page 2504, third full paragraph).

As evident from the overlap between the drugs suitable for treatment of partial seizures and the drugs suitable for treatment of generalized seizures, many of the mechanisms by which partial seizures and generalized seizures can be treated must also overlap.

Professor Marson states that he fully agrees with these conclusions. (**Exhibit 1002**, ¶ 63).

In summary, these prior art references clearly teach the use of CBD to treat seizures without significant side effects; suggest the increase in CBD dosages to treat seizures when the lower dosage of 200-300 mg per day was not effective; and demonstrate a significant overlap between drugs suitable to treat different types of seizures. Accordingly, PHOSITA would have found it obvious to use CBD for the

treatment of partial seizures at the daily dosage of at least 400 mg with a reasonable expectation of success.

3. Dependent Claims 2-13

Dependent claims 2-13 are obvious over Cunha *et al* in view of Bhattacharyya *et al*, Ames *et al*, Lowenstein and WO '697 for at least the same reasons that independent claim 1 is obvious over these references. There is nothing in these dependent claims that would overcome the obviousness over the cited art.

Specifically, claim 2 further specifies a daily dose of CBD to be from 400 mg to 800 mg. But as the Petitioner has shown, it would have been obvious to adjust the dosages based on the disclosure of the references. There is not any additional data or evidence specific to the range of 400-800 mg of CBD per day.

Claims 6-9 introduce additional limitations, such as CBD being a plant extract (claim 6); the plant extract comprising less than 5% by weight of THC (claim 7); the plant extract comprising less than 1% by weight of THC (claim 8); and CBD being a pure or isolated cannabinoid (claim 9). All of these limitations are obvious to a person of ordinary skill in the art for all the same reasons stated above.

Dependent claims 3-5 and 10-13 differ from the subject matter of independent claim 1 and dependent claims 2 and 6-9 in that dependent claims 3-5

and 10-13 all require that the CBD be used in combination with tetrahydrocannabivarin (THCV). (**Exhibit 1001**, 15:10-16; 16:7-21).

All of these claims are invalid as obvious for the same reasons as outlined in Ground I and for the additional reason that WO '697 teaches that CBD and THCV should be combined for the treatment of various disorders, including epilepsy. (**Exhibit 1020**; Abstract; page 3, lines 9-18).

Accordingly, there is nothing in dependent claims 2-13 that would render the subject matter of these claims non-obvious over Cunha *et al* in view of Bhattacharyya *et al*, Ames *et al*, Lowenstein and WO '797.

C. Ground II: Independent Claim 1 and Dependent Claims 2-13 Are Obvious Under §103(a) Over Cunha *et al* in View of Pertwee, Malfait *et al*, Lindamood *et al*, Mechoulam *et al*, Zuardi *et al* and WO 2009/007697.

1. Brief Summary of Ground II Arguments

Ground II of this IPR Petition relies on the same primary reference as Ground I (Cunha *et al*) but additionally provides expert testimony by Professor Benet relying, in part, on the additional different secondary references: Pertwee, Malfait *et al*, Lindamood *et al*, Mechoulam *et al*, and Zuardi *et al*, as well as on the

same reference WO 2009/007697. If there is any doubt that claimed CBD dosage was not clearly suggested as obvious in Ground I, this expert declaration establishes without doubt that it was obvious to increase the dosage of CBD to arrive at the claimed dosage.

2. Availability of References As Prior Art

The availability of Cunha *et al* and WO 2009/007697 is explained in the Section XII.B.1 of this Petition.

Pertwee is Chapter 3, "The Pharmacology and Therapeutic Potential of Cannabidiol," pp32-83 in the book *Cannabinoids,* Ed Vincenzo Di Marzo Springer Science & Business Media, (2004) (**Exhibit 1022**).

Malfait *et al* is a scientific article published in Proceedings of National Academy of Sciences (PNAS), August 15, 2000, Vol. 97, No. 17, pp. 9561-9566. (**Exhibit 1023**). Accordingly, Malfait *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

Lindamood *et al* is a scientific article published in The Journal of Pharmacology and Experimental Therapeutics, Vol. 213, No. 2, pp. 216-221 in 1980. (**Exhibit 1024**). Accordingly, Lindamood *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

Mechoulam *et al* is a scientific article Cannabidiol: An Overview of Some Pharmacological Aspects, published in *J Clin Pharmacol*, **42:** 11S-19S in 2002. (**Exhibit 1021**). Accordingly, Mechoulam *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

Zuardi *et al* is a scientific article published in Rev Bras Psiquiatr. 30(3): 217-80 in 2008. (**Exhibit 1025**). Accordingly, Zuardi *et al* is available as prior art under at least 35 U.S.C. §102(b) (pre-AIA).

3. Independent Claim 1

Claim 1 is directed to a method of treatment of partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

The prior art teaches or suggests all elements of this claim.

Cunha *et al* Teaches Treatment of the Same Disease with the Same Drug

Cunha *et al* is a study of 15 patients suffering from "secondary generalized epilepsy with temporal focus". (**Exhibit 1004**, Abstract).

As Professor Marson explains, it is clear from the ILAE classification and from the explanatory tables in Dreifuss *et al* (**Exhibit 1007**, pages 493-495) that the 15 patients suffering from "secondary generalized epilepsy with temporal

focus" are classified as patients having partial seizures. (**Exhibit 1002**, ¶ 50). These seizures had a focal onset as evidenced by the phrase "secondary generalized epilepsy with temporal focus" and therefore, under the ILAE classification, these patients must be classified as suffering from partial seizure.

As explained in Section VIII.A.3 of this Petition, "partial seizures" consist primarily of three main types: 1) simple partial seizures; 2) complex partial seizures; and 3) partial seizures evolving to secondary generalized seizures. Thus, Cunha *et al* disclose the treatment of a species of the genus of "partial seizures" (wherein the "partial seizures evolving to secondary generalized seizures" is the species).

Despite the Patentee's attempt to re-define the "partial seizure" as a seizure that originates in specific brain regions and remains localized, the term "partial seizure" must be construed consistently with the ILAE definition, as a seizure that originates in specific brain regions, whether or not it remains localized. As Insys has explained in Section IX of this Petition:

1) The ILAE classification clearly distinguishes between seizures that are generalized from the beginning and those that are partial or focal at onset (i.e. at the beginning) and may become generalized secondary. (**Exhibit 1002**, ¶ 19).

2) Contrary to the patentee's statement, neither McCormick and Contreras

nor Lutz (the references that allegedly stated that partial seizures remain localized) ever state that partial seizures remain localized. (**Exhibit 1002**, ¶¶ 36-40).

3) Dr. Lowenstein explains that partial seizures with secondary generalization fall within the group of "partial seizures" and that it is important to distinguish primary generalized seizures from secondary generalized seizures. (**Exhibit 1019**, Table 363-1 on page 2498, and page 2499, the paragraph bridging the left-hand and the right-hand columns).

4) The Patentee did not give any notice or explanation that its definition of the term "partial seizures" differs from the widely accepted definition, and in fact created the incorrect impression that its definition is the same as the ILAE definition.

Thus, under the proper claim construction of the term "partial seizure," Cunha *et al* disclose the use of the same drug (CBD) to treat the same disease (partial seizure) as the method recited in claim 1.

Accordingly, the only difference between the disclosure of Cunha *et al* and the method recited in claim 1 of the '920 patent is the recited daily dosage of at least 400 mg.

Cunha *et al* disclose administering 200-300 mg CBD per day to patients with partial seizures with successful results

Cunha *et al* report that of the eight patients who received CBD, at dosages of 200-300 mg per day, four patients demonstrated almost complete improvement, three demonstrated partial improvement, and one remained unchanged. (**Exhibit 1004**, Abstract). In contrast, out of the eight patients who received a placebo (one patient was both a placebo patient and then a CBD patient), only one patient improved, while seven had no improvement.

Cunha *et al* also disclose that CBD was administered at dosages "roughly corresponding to 200-400 mg/subject" to healthy volunteers without any serious side effects or toxicities. It is undisputed that the claimed amount "which provides a daily dose of at least 400 mg" falls within the range disclosed in Cunha *et al*.

The Claimed Daily Dosage of At Least 400 mg CBD Is Predictable and Expected

It would be routine and obvious to a PHOSITA to arrive at the claimed dosage of at least 400 mg.

As Professor Benet explains, in seizures, CBD has a conventional sigmoidal dose response curve, meaning that CBD response increases with dose increases.

(**Exhibit 1003**, ¶ 14). Therefore, a PHOSITA would have expected that, when used for the treatment of seizures, CBD response would increase with dose in a monophasic fashion.

This is demonstrated, for example, by Lindamood *et al* and Wallace *et al*, which describe maximal electroshock seizure (MES) studies in rats and mice, respectively.

Professor Benet explains that the MES model is currently the best available model for identifying and testing anticonvulsant compounds, i.e. drugs to treat seizure. (**Exhibit 1003**, ¶ 17; see also, Castel-Branco (2009) (**Exhibit 1028**), page 101, first full paragraph in the right-hand column). According to Professor Benet, MES is the best model for evaluating drugs for partial seizures, including secondary generalized seizures, simple partial seizures and complex partial seizures. (**Exhibit 1003**, ¶ 17).

Lindamood *et al* (**Exhibit 1024**) describes MES studies in rats, whereby CBD doses of 45, 60 and 75 mg/kg were administered. The ED_{50} value for CBD (i.e., the "median effective dose" or the dose that produces a desired effect in 50% of the population) was determined to be 52.1 mg/kg. The dose response curve is monophasic and not bell-shaped. (**Exhibit 1003**, ¶¶ 18-19).

Wallace *et al* (**Exhibit 1027**) describes MES mouse model of partial seizures which also demonstrates a conventional dose response curve where CBD response increased with dose in a monophasic fashion. (**Exhibit 1003**, ¶¶ 20-21).

Therefore, as Professor Benet explains, the prior art establishes that a person of ordinary skill in the art would expect the response to CBD to increase when the dosage of CBD is increased from 300 mg daily (dosage in the studies of Cunha *et al*) to more than 400 mg daily. (**Exhibit 1003**, ¶ 23).

To figure out an optimal dose of CBD to administer to human patients with partial seizures, a PHOSITA could turn to Pertwee (**Exhibit 1022**).

Pertwee teaches that:

> "It is also noteworthy that in mg/kg terms, drugs are often more potent in man than in rats or mice as they are more rapidly metabolized by these smaller species. When allowance is made for these differences in metabolic rate, anticonvulsant CBD doses of 12mg/kg in 250g rats and 80 mg/kg in 25g mice (Table 4) correspond approximately to 144 mg (2.2 mg/kg) and 445 mg (96.8 mg/kg) respectively in 65 kg human subjects." (**Exhibit 1022**, page 72).

As Professor Benet explains, Pertwee does not specify the route of administration for these anticonvulsant doses in human subjects. However, in

previous studies, CBD was given orally or intraperitoneally (i.p.). (**Exhibit 1003**, ¶¶ 30-31).

However, CBD has a poor oral bioavailability. This is shown in the studies of Mechoulam *et al* (**Exhibit 1021**), Malfait *et al* (**Exhibit 1023**), and Consroe *et al* (**Exhibit 1026**)). Mechoulam *et al* teach that oral bioavailability of CBD is between 13% and 19%. (**Exhibit 1021**, page 12S). Malfait *et al* demonstrate that a maximum i.p. dose of CBD is equivalent to an oral dose of 25 mg/kg, suggesting an oral bioavailability of 20%. Consroe *et al* show that CBD in the rat MES, when dosed orally, has an ED_{50} of 12 mg/kg, equivalent to a dose of 115 mg in a 60 kg human. (**Exhibit 1026**). See, also, **Exhibit 1003**, ¶¶ 24-28.

Because CBD has poor oral bioavailability, larger doses are required for oral administration to achieve the equivalent effect to intraperitoneal administration. (**Exhibit 1003**, ¶ 26).

As Professor Benet explains, a PHOSITA would believe that the oral dose of CBD a 65kg human subject corresponding to an i.p. dose of 80mg/kg in mice is about $445 \div 0.20 = 2225$ mg. (**Exhibit 1003**, ¶ 33).

In other words, a PHOSITA reading Pertwee, Mechoulam *et al* and Malfait *et al* together would realize that, based on the rat and mouse studies, a potential

oral anticonvulsant dose of CBD in a 65 kg human subject lies between 144 mg and 2225 mg. (**Exhibit 1003**, ¶ 34).

As Professor Benet explains, it is clear from Lindamood *et al* that at these doses, which are at middle of the range of dose response curve, response increases with dose. (**Exhibit 1024**, pages 217-218; **Exhibit 1003**, ¶ 35).

Furthermore, Zuardi *et al* teaches that CBD has been administered at oral doses of up to 1500 mg/day without significant side effects. (**Exhibit 1025**, page 274).

Therefore, it would have been obvious for a PHOSITA to increase the oral dose of CBD from the disclosed 200-300mg/day to over 400mg/day for the treatment of partial seizures.

4. Dependent Claims 2-13

Dependent claims 2 and 6-9 are obvious over Cunha *et al* in view of Pertwee, Malfait *et al*, Lindamood *et al*, Mechoulam *et al*, and Zuardi *et al*. Mechoulam *et al* for at least the same reasons that independent claim 1 is obvious over these references. There is nothing in these dependent claims that would overcome the obviousness over the cited art.

Dependent claims 3-5 and 10-13 differ from the subject matter of independent claim 1 and dependent claims 2 and 6-9 in that dependent claims 3-5 and 10-13 all require that the CBD be used in combination with tetrahydrocannabivarin (THCV). (**Exhibit 1001**, 15:10-16; 16:7-21).

All of these claims are invalid as obvious for the same reasons as outlined in Ground II and for the additional reason that WO '697 teaches that CBD and THCV should be combined for the treatment of various disorders, including epilepsy. (**Exhibit 1020**; Abstract; page 3, lines 9-18).

Accordingly, for all of these reasons, claims 2-13 are obvious over Cunha *et al* in View of Pertwee, Malfait *et al*, Lindamood *et al*, Mechoulam *et al*, Zuardi *et al*. and WO '797.

D. Ground III: Independent Claim 1 and Dependent Claims 2-13 Are Obvious Under §103(a) Over Jones *et al* in View of Cunha *et al*, Lowenstein and WO 2009/007697.

1. Brief Summary of Ground III Arguments

Ground III of this IPR Petition relies on a more recent (published in 2010) primary reference: Jones *et al*, and on the same references of Cunha *et al*, Lowenstein and WO 2009/007697. Jones *et al* teaches the use of CBD to treat partial seizures and further teaches that dosages of up to 600 mg (which

encompasses the claimed dosages "a daily dose of at least 400 mg are well tolerated in humans. Combining Jones *et al* with the other references discussed in detail in Grounds I and II of this Petition further reaffirms that even contemporary prior art renders the claims of the '920 patent obvious.

2. Availability of References As Prior Art

The availability of Cunha *et al,* WO '697 and Lowenstein is explained in the Section XII.B.1 of this Petition.

Jones *et al* is a scientific article which was published in the Journal of Pharmacology and Experimental Therapeutics on November 11, 2009 (e-publication). (**Exhibit 1018**). Accordingly, Jones *et al* is available as prior art under at least 35 U.S.C. §102(a) (pre-AIA).

3. Independent Claim 1

Claim 1 is directed to a method of treatment of partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

The prior art teaches or suggests all elements of this claim.

Jones *et al* disclose that CBD displays anti-seizure properties in vitro and in vivo. (**Exhibit 1018**, page 569, Abstract). Jones *et al* state that they "demonstrate the potential of CBD as a novel antiepileptic drug in the unmet clinical need

associated with generalized seizures." (**Exhibit 1018**, page 569, Abstract).

Furthermore, Jones *et al* state that "CBD has been reported to have relatively potent anticonvulsant action in maximal electroshock (a model of partial seizure with secondary generalization) (Karler *et al.*, 1974; Consroe and Wolkin 1977)." (**Exhibit 1018**, page 576, first full paragraph).

Jones *et al* disclose that CBD demonstrated anticonvulsant activity at 100 mg/kg in rats (**Exhibit 1018**, page 576, first full paragraph). Assuming a rat/human conversion factor of x6 (as taught in the '920 patent; **Exhibit 1001**; 13:35-38), this suggests a CBD daily dose of at least 600 mg.

Citing Bhattacharyya *et al*, Jones *et al* teach that that CBD is extremely well tolerated in humans. (**Exhibit 1018**, page 570, first paragraph).

Thus, Jones *et al* establish that: 1) CBD displays anti-seizure/anti-convulsant properties; 2) at dosages corresponding to 600 mg daily dose in humans; 3) has been shown to be effective in animal model of partial seizure with secondary generalization; 4) can be used to treat generalized seizures; and 5) is very well tolerated in humans.

As explained in detail in the section of this Petition dealing with Ground I, Cunha *et al* teach the use of CBD to treat secondary generalized seizures (*i.e.*, partial seizures); teach the treatment of secondary generalized seizures with 200-

300 mg daily dosages of CBD; and teach that the CBD had a safe profile with no significant side effects. (**Exhibit 1004**, Abstract; page 177, top left-hand column; page 182, second paragraph in the right-hand column).

As explained in detail in the section of this Petition dealing with Ground I, Lowenstein teaches that there is a large overlap between the drugs which are used to treat partial seizures and the drugs that are used to treat generalized seizures. (**Exhibit 1019**, pages 2507-2509). Lowenstein also explains that many of the mechanisms by which antiepileptic drugs work would be expected to treat both partial and generalized seizures.

As evident from the overlap between the drugs suitable for treatment of partial seizures and the drugs suitable for treatment of generalized seizures, the mechanisms by which partial seizures and generalized seizures can be treated must also overlap.

Further, there is not any evidence of unexpected results or teaching away from the invention.

Accordingly, based on Jones *et al* and in view of Cunha *et al* and Lowenstein, a PHOSITA would have found it obvious to use CBD for the treatment of partial seizures at the daily dosage of at least 400 mg with a reasonable expectation of success.

4. Dependent Claims 2-13

Dependent claims 2 and 6-9 are obvious over Jones *et al* in view of Cunha *et al* and Lowenstein for at least the same reasons that independent claim 1 is obvious over these references. There is nothing in these dependent claims that would overcome the obviousness over the cited art.

Dependent claims 3-5 and 10-13 differ from the subject matter of independent claim 1 and dependent claims 2 and 6-9 in that dependent claims 3-5 and 10-13 all require that the CBD be used in combination with tetrahydrocannabivarin (THCV). (**Exhibit 1001**, 15:10-16; 16:7-21).

All of these claims are invalid as obvious for the same reasons as outlined in Ground III and for the additional reason that WO '697 teaches that CBD and THCV should be combined for the treatment of various disorders, including epilepsy. (**Exhibit 1020**; Abstract; page 3, lines 9-18).

Accordingly, for all of these reasons, claims 2-13 are obvious over Jones *et al* in view of Cunha *et al*, Lowenstein, and WO '797.

XIII. CONCLUSION

All of the claims of the '920 patent are obvious over the prior art.

The use of CBD to treat seizures has been known since at least 1980, as reported by Cunha *et al*. CBD was also known to treat partial seizures including

secondary generalized seizures. The only difference between the subject matter of the '920 patent and the prior art is that the prior art does not explicitly teach the recited daily dosage of at least 400 mg of CBD for the treatment of partial seizure. However, it would have been obvious to a PHOSITA to treat partial seizures with CBD at the claimed amount because: 1) it was well known that CBD was extremely well tolerated in humans, 2) it was well within a skill in the art to optimize a treatment dosage, 3) the prior art, such as Ames *et al*, expressly suggested to increase the CBD dose for the treatment of seizures; and 4) CBD in seizure models shows response increase with dose in a monophasic fashion.

Furthermore, the patentee admits that CBD was known to treat seizures. Because anticonvulsant properties of CBD were well known and because there is a very significant overlap between the drugs that treat generalized seizures and partial seizures, it would have been obvious to a PHOSITA that CBD could effectively treat partial seizures with a reasonable expectation of success.

Finally, the USPTO Examiner only allowed the claims to issue based on a mistaken belief that a prior art reference directed to cannabinoid liquid formulations teaches away from the claimed invention. The reference clearly does not teach away from the invention, but instead teaches how to better solubilize large doses of CBD.

For all the reasons stated above, it was obvious that a skilled artisan could easily adjust the dosage of CBD to arrive at the claimed dosage with a reasonable expectation of success. Accordingly, the patent must be invalidated in its entirety.

CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, the undersigned certifies that on the 16th day of December, 2016, a complete and entire copy of the PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,066,920 ("Petition") including exhibits and testimony relied upon were served on the patent owner at the correspondence address of record for the subject patent,

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