UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INSYS DEVELOPMENT COMPANY, INC.
Petitioner

v.

GW PHARMA LIMITED ET AL.
Patent Owners

Case IPR2017-00503
Patent 9,066,920

PATENT OWNERS' PRELIMINARY RESPONSE

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LIST OF EXHIBITS

Exhibit No.	Description
2001	Mares et al., *Electrical Stimulation-Induced Models of Seizures in Model of Seizures and Epilepsy* (Asla Pitkänen, Philip A. Schwartzkroin & Solomon L. Moshé, eds.), 2004
2002	Izzo et al., Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb, 30 Trends in Pharmacological Sciences 515 (2009)
2003	Turkanis et al, *An Electrophysiological Analysis of the Anticonvulsant Action of Cannabidiol on Limbic Seizures in Conscious Rats*, 20 Epilepsia 351 (1979)
2004	Guimaraes et al., *Antianxiety effect of cannabidiol in the elevated plus-maze*, 100 Psychopharmacology 558 (1990)
2005	Braida et al., *Post-ischemic treatment with cannabidiol prevents electroencephalographic flattening, hyperlocomotion and neuronal injury in gerbils*, 346 Neuroscience Letters 61 (2003)

I. INTRODUCTION

The inventors of U.S. Patent 9,066,920 ("the '920 patent") discovered that cannabidiol (CBD) at specific doses could be successfully used to treat epilepsy patients experiencing a specific category of seizures. Epilepsy is a neurological disorder presenting a wide spectrum of diseases. EX. 1001, 1:20-21. In fact, there are more than forty recognizable types of epileptic syndrome partly due to seizure susceptibility varying from patient to patient, making it a challenge to find effective drugs. EX. 1001, 2:26-30. These seizures are generally grouped into two categories: partial seizures and generalized seizures. EX. 1001, 2:31-35. The '920 patent discloses and claims methods for treating a specific category of seizures—partial seizures—by administering CBD in a daily dose of at least 400 mg.

CBD, like other cannabinoids, has a complex pharmacology, acting through at least 22 different molecular mechanisms. EX. 2002 (Izzo), pp. 5-6. Many of CBD's effects were known to display a bell-shaped dose-response curve, where higher doses would actually show no effect at all. EX. 1025 (Zuardi), p. 7. Before the '920 patent's filing date, however, very little was known regarding the dose-response relationship for CBD in treating seizures and, in particular, partial seizures. Testing from an animal model of partial seizures, the limbic seizure model, suggested that CBD's effect against partial seizures might display a bell-

shaped dose-response curve. EX. 2003 (Turkanis), p. 8. Testing from another animal model of generalized seizures, the maximal electroshock ("MES") model, showed CBD seeming to have an effect, but other testing using the MES model with similar doses showed CBD had no effect. *Compare* EX. 1022 (Pertwee), Table 4, pp. 19-20 ("Behavioural models of epilepsy in which CBD shows activity") with Table 6, pp. 22-23 ("Models of epilepsy in which CBD lacks detectable activity"). The animal models simply lacked any clarity on dose response for treatment of partial seizures.

The lack of meaningful clinical data before the '920 patent's filing date compounded this uncertainty. Before the inventors made their discovery, there were few controlled trials that had investigated the anti-epilepsy potential of CBD. EX. 1001, 1:58 to 2:10. And many of those studies were years earlier. As the '920 patent notes, "[i]t is perhaps significant that some 20 years since these trials there has been no further development." *Id.,* 2:11-12. Against this backdrop, the inventors discovered that daily doses of CBD in excess of 400 mg could successfully treat partial seizures.

Petitioner challenges the '920 patent claims as obvious based upon three grounds. Each ground is deficient.

Grounds I and II of the Petition rely upon Cunha (EX. 1004) as the primary reference. Cunha describes an early-stage clinical trial, summarized in the '920

patent, that investigated the use of 200-300 mg/day doses of CBD co-administered with other anticonvulsant medications to treat seizures in a limited number of patients. EX. 1001, 1:62-2:2. Cunha concluded that CBD "had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal focus," but could not identify the mechanism responsible for the benefit, and emphasized that "[f]urther research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans." EX. 1004 (Cunha), p. 9.

Cunha provides no reason why increasing the CBD dosage would be beneficial for treating partial seizures. In Grounds I and II, Petitioner attempts to address this deficiency through five- and seven-way obviousness combinations, respectively. Both attempts fail. Each ground ignores or mischaracterizes the existing state of the art relating to the use of CBD to treat seizures. Neither offers a reasoned rationale as to why, given the limited and contradictory information available regarding CBD doses for treating any kind of seizure, a person of ordinary skill would have been motivated to increase Cunha's dosage with the reasonable expectation that it could successfully treat partial seizures. At best, the prior art was an array of inconclusive and contradictory teachings that did not allow for any reasonable expectation of success with respect to dosage.

Ground III of the Petition relies on a different primary reference, Jones (EX. 1018), but fails to establish that it is prior art. Ground III also fails for a separate reason: it does not offer any articulated reasoning why a skilled artisan would have selected the teaching of Jones and combined it with the three additional relied-upon references to achieve the claimed invention with a reasonable expectation of success. Notably, Petitioner offers no expert testimony to support its arguments in Ground III.

Finally, independent of the Board's decision on whether to institute on any of the three grounds with respect to claim 1 of the '920 patent, Petitioner fails to present anything other than conclusory argument for why dependent claims 3-13 would have been obvious. The Petition fails even to identify where the prior art teaches most of the additional limitations.

For at least these reasons, Petitioner has failed to demonstrate a reasonable likelihood that claims 1-13 of the '920 patent are unpatentable as obvious. The Petition should be denied.

II. BACKGROUND

A. CBD Has a Complex Pharmacological Profile and Many of Its Effects Were Known to Display a Bell-Shaped Dose-Response Curve.

CBD has a wide range of pharmacological effects in both the central nervous system and the periphery, including acting as a neuroprotective agent and treating

epilepsy, glaucoma, central and peripheral inflammatory disorders, anxiety, acute schizophrenia, dystonia, nausea, and cancer.[1] EX. 1022 (Pertwee), p. 4. CBD acts through multiple mechanisms, each with its own concentration dependence. To achieve its many pharmacological effects, CBD can act on "various receptor types, both established and postulated, release processes for certain neurotransmitters and cytokines, receptor signaling mechanisms, membrane transporters, and enzymes responsible for catalyzing the biosynthesis and/or metabolism of prostaglandins, endogenous cannabinoids and other eicosanoids." *Id.* CBD's numerous pharmacological effects, and the great number of molecular mechanisms it uses to achieve those effects, can be seen in Figure 1 of Izzo (EX. 2002), p. 11:

[1] Unlike Δ^9-tetrahydrocannabinol (Δ^9-THC), which is the main psychoactive plant cannabinoid, CBD is not psychoactive. EX. 1022 (Pertwee), p. 4.

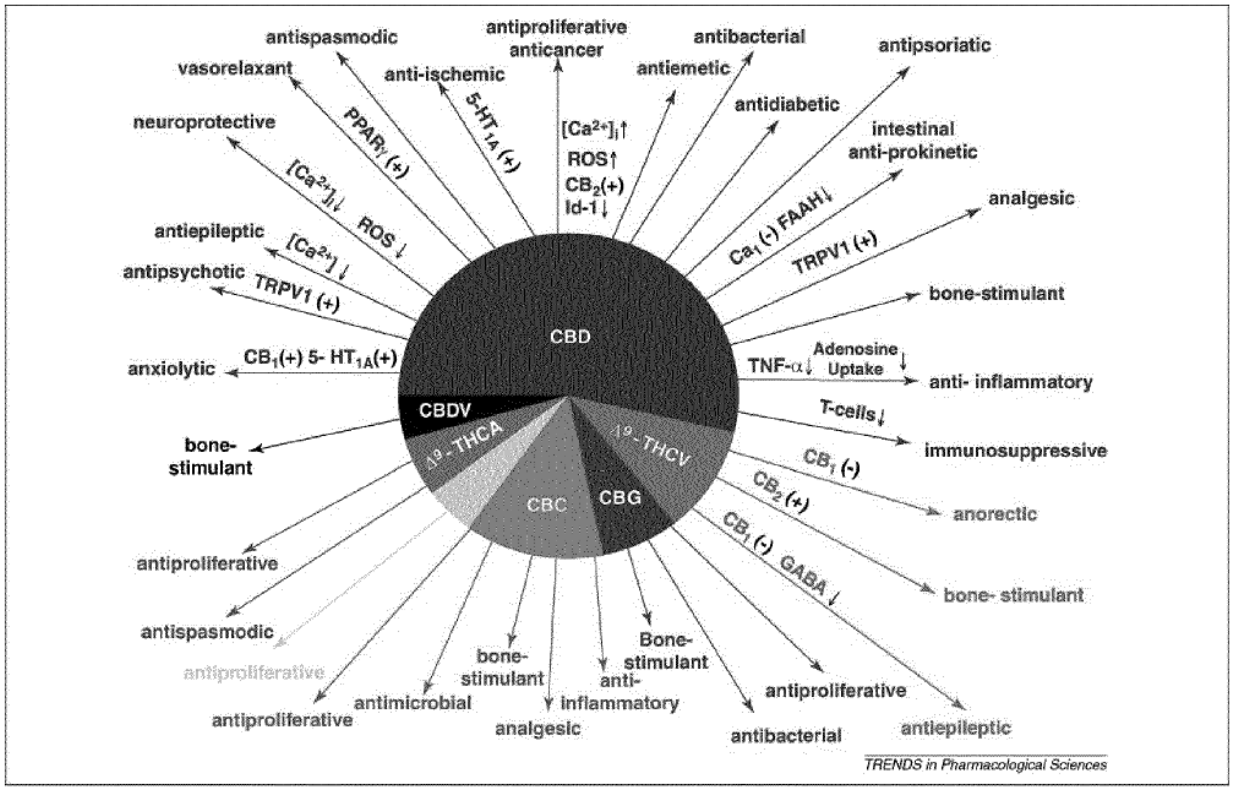

Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).

As of the priority date of the '920 patent, CBD had at least 22 proposed molecular mechanisms of action. *See id.* at pp. 5-6 (Table 1 describing CBD's proposed molecular mechanisms of action).

Because CBD acts through multiple mechanisms, dose is a "pivotal factor" in whether CBD produces a particular pharmacological effect. *See* EX. 1025 (Zuardi), p. 7; *see also* EX. 2010 (Izzo), p. 7 ("dose is a key factor in CBD pharmacology"). CBD's multiple mechanisms of action can work in opposing ways—one stimulating a given effect and another suppressing it. *See* EX. 1022 (Pertwee), p. 38. Accordingly, whether a dose of CBD is effective for a given pharmacological effect depends not only on which mechanisms of action ***are***

activated, but also on which mechanisms ***are not*** activated. *See, e.g.*, *id.* (describing how a particular effect of CBD "fades away at higher doses," because those higher doses begin to activate two molecular mechanisms that oppose the effect).

Because of these complex interactions, many effects of CBD were known to display a bell-shaped (or biphasic) dose-response curve—*i.e.*, increasing the dose of CBD could actually decrease the effect. EX. 1025 (Zuardi), p. 7 ("many effects of CBD draw a bell-shaped curve, suggesting that the dose is a pivotal factor in CBD research"). For example, CBD's anti-anxiety (or anxiolytic) effect had a "narrow" range of effective doses, above which CBD was "no longer effective" to manage anxiety. *See* EX. 2004 (Guimaraes), p. 2. Two other effects, the anti-inflammatory and neuroprotective effects, were also known to display bell-shaped dose-response curves. *See* EX. 1023 (Malfait), p. 1 ("The dose dependency [of CBD's anti-inflammatory effect] showed a bell-shaped curve, with the 5 mg/kg dose exerting an optimal therapeutic benefit, whereas both the lowest dose (1.5 mg/kg) and the highest dose (20 mg/kg) were inactive."); EX. 2005 (Braida), Fig. 1(A) (charting the bell-shaped dose-response for curve CBD's neuroprotective effect). Because of CBD's complex pharmacology and known bell-shaped dose response curves, a person of skill would have known before the '920 patent's filing

date that raising the dose of CBD might decrease, rather than increase, CBD's effect on partial seizures.

B. The Animal Models Used to Test the Efficacy of CBD for Treating Partial Seizures Were Inconclusive Yet Suggested CBD Might Have a Bell-Shaped Dose-Response Curve.

Various animal models are used to screen potential treatments for the different types of epileptic syndrome. *See, e.g.*, EX. 1028 (Castel-Branco), p. 1. In the case of CBD, the animal models provided inconclusive and contradictory results. However, the model most closely associated with partial seizures, the limbic model, suggested that increasing the dose of CBD would decrease efficacy. *See* EX. 2011 (Turkanis), p. 8.

Epilepsy is a neurological disorder characterized by seizures that generally are grouped into two categories: partial seizures and generalized seizures. EX. 1001, 2:31-35; EX. 1008 (McCormick), p. 1. Partial seizures occur within a localized area of the brain, whereas generalized seizures appear throughout the forebrain. EX. 1008 (McCormick), pp. 1-2. According to the International League Against Epilepsy (ILAE), partial seizures can be further classified into three fundamental groups. EX. 1009, p. 5. First, there are simple partial seizures, which do not cause a disruption of consciousness or cognitive abilities. *Id.*; *see also* EX. 1008 (McCormick), p. 2. Second, there are complex partial seizures, which do cause a disruption of consciousness or cognitive abilities. *Id.* Third, according to

the ILAE, there are secondary generalized seizures, which start as a localized partial seizure, either simple or complex, and evolve into a general seizure that affects the entire forebrain. *Id.*

Researchers used animal models of seizure for the initial *in vivo* testing of potential anti-seizure drugs, with different animal models mimicking different types of seizure. *See, e.g.*, EX. 1028 (Castel-Branco), p. 1. For example, the Maximal Electroshock (MES) model was used to evaluate whether drugs might be effective against generalized seizures of the tonic-clonic (grand mal) type. *Id.*; *see also* EX. 2001 (Mares), p. 1 ("Maximal electroshock seizures (MESs) are a model of generalized tonic-clonic seizures."). Wallace (EX. 1027) suggested that the MES model could be used to evaluate drugs for treating secondary generalized seizures. EX. 1027 (Wallace), p. 1. Nevertheless, the literature recognized that because the MES model was a model of generalized seizures, "the MES test can fail to identify drugs that are clinically effective in treating partial seizures." EX. 2001 (Mares), p. 5. Pertwee (EX. 1022), as discussed below, reported contradictory results for CBD treatment of seizures—some studies showing an effect and other studies showing no effect—using the MES model.

The limbic seizure model used in Turkanis was "considered to be closely associated with complex partial seizures." EX. 2011 (Turkanis), p. 10. In the limbic seizure model, a model of partial seizures, CBD seemed to display a bell-

shaped dose-response. The paper reports that CBD displayed a "significant[]" anti-seizure effect "at low doses … but not at high doses." *Id.,* p. 8. The authors could not explain why CBD showed less anti-seizure activity at higher doses, but said that the "cannabinoids … have been reported to cause qualitatively different responses as a function of dose." *Id.*

Prior to the '920 patent's filing date, there was nothing in the prior art animal studies teaching what dose of CBD, if any, would effectively treat partial seizures.

C. There Was Little Clinical Data on CBD's Ability to Treat Partial Seizures Before the Invention.

Before the '920 patent's filing date, there were few controlled trials that had investigated the anti-epilepsy potential of CBD. EX. 1001, 1:58 to 2:10. Two of the references upon which Petitioner relies, Cunha (EX. 1004) and Ames (EX. 1011), describe two of the early studies.

Cunha describes a 1980 clinical study in which 15 patients suffering from secondary generalized epilepsy with temporal focus were divided into two groups. EX. 1004 (Cunha), p. 1. One group (eight patients) was given 200-300 mg of CBD daily for four and a half months, while the other group (seven patients) was given placebo. *Id.* Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. *Id.* Cunha states that out of the eight

patients receiving CBD, four patients "remained almost free of convulsive crises throughout the experiment," three other patients demonstrated "partial improvement," and one patient demonstrated no effect. *Id.* Cunha noted that the mechanism by which CBD benefitted patients was unknown but could have been due to the enhancement of the other antiepileptic drugs' anticonvulsant activity or attributable to CBD itself. *Id.,* p. 9. On the basis of this limited study, Cunha concluded that "CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal focus, who did not benefit from known anti-epileptic drugs." *Id*. However, Cunha made clear that "[f]urther research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans." *Id.*

Ames describes a 1985 study involving a unique class of twelve patients "who were institutionalized because of mental retardation and also had frequent seizures who were not controlled on conventional anti-convulsant therapy …." EX. 1011 (Ames), p. 1. Ames provided no further information regarding the patients' epilepsy. In particular, Ames did not disclose whether the patients suffered from generalized seizures or partial seizures.

One group of Ames' patients received 300 mg of CBD per day for one week (3 capsules, each containing 100 mg CBD) and then 200 mg of CBD per day for

the next three weeks (2 capsules, each containing 100 mg CBD). *Id.* The second group received placebo. *Id.*

Ames noted that there was no "statistically significant difference in seizure frequency between the two groups." *Id.* In other words, CBD was ineffective. Ames proposed increasing the dose, speculating that "[CBD's] lack of efficacy might have been due to the fact that the patients were all brain-damaged and severely epileptic." *Id.* However, Ames did not state what the increased dose would be. Ultimately, Ames abandoned the study after being unable to obtain more CBD. *Id.*

Both the Cunha and Ames' studies involved a limited number of patients. Ames' patients, in particular, were a unique subset of severely disabled patients. And while Cunha disclosed that the patients suffered from secondary generalized epilepsy with temporal focus, Ames disclosed nothing regarding the type of seizures the subjects were experiencing. Cunha and Ames underscore how little was known regarding the ability of CBD to treat any type of seizures, let alone the dose-response relationship between CBD and partial seizures, before the '920 patent's filing date.

III. THE '920 PATENT

The '920 patent recites methods for treating partial seizures by administering CBD to a patient at a particular dosage. Claim 1, the only independent claim,

requires administering a daily dose of at least 400 mg. A dependent claim further limits the daily dose to from 400 to 800 mg. *See* '920 patent, claim 2.

The '920 patent specifically identifies the findings of Cunha (EX. 1004) and Ames (EX. 1011), *see* EX. 1001, 1:62-2:26, adding that "[i]t is perhaps significant that some 20 years since these trials there has been no further development." *Id.* at 2:11-12. As the '920 patent describes, one explanation for the extended delay is that dose is a critical factor that neither Cunha nor Ames adequately resolved. *See id.* at 2:15-18 ("It is also possible that the dose levels used in the trials were not optimal and the applicant has determined that cannabinoids may produce bell shaped dose response curves.").

A first set of dependent claims of the '920 patent further requires that the claimed dosage of CBD be administered in combination with tetrahydrocannabivarin (THCV). *See id.* at claim 3. Additional claims further require administering THCV at a particular daily dosage, *see id.* at claim 4 (a daily dose of THCV of at least 1.5 mg); *id.* at claim 5 (a daily dose of THCV of at least 15 mg).

A second set of dependent claims requires that the CBD is present as a plant extract. *See, e.g., id.* at claim 6. Claims in this series also require that, where the CBD is present as plant extract, the plant extract comprises less than a certain percentage by weight of tetrahydrocannabinol (THC) of any cannabinoids present

in the plant extract. *See id.* at claims 7 and 11 (THC must be less than 5% by weight of any cannabinoids present); *id.* at claims 8 and 12 (THC must be less than 1% by weight of any cannabinoids present). These claims reflect, as the '920 patent describes, that "the results with pure CBD suggest that an extract containing significant amounts of both THCV and CBD, but again, minimal or substantially no THC may provide an optimum combination." *Id.* at 13:19-23.

A third set of dependent claims combines the first two: CBD is administered with THCV and is present as a plant extract. *See, e.g., id.* at claim 10. Claims in this set also contain limitations concerning the amount of THC present in the plant extract, requiring less than 5% (claim 11) or 1% (claim 12) by weight.

Finally, two dependent claims require that CBD "is present as a pure or isolated cannabinoid." *Id.* at claims 6 and 13.

IV. CLAIM CONSTRUCTION

Each of the '920 claims recites a method for treating "partial seizures." Petitioner proposes construing "partial seizures" to include secondary generalized seizures. Petition, p. 18. However, even under its preferred construction of the term "partial seizures," Petitioner fails to meet its burden to show that a person of ordinary skill would have been motivated to increase the dosage of CBD administered by Cunha (EX. 1004) and would have reasonably expected that higher dosage to treat partial seizures. Accordingly, it is not necessary to construe

the term "partial seizures" to deny institution. *See Bayer CropScience AG v. Dow AgroSciences LLC*, 728 F.3d 1324, 1331 ("this court has limited its claim construction analysis to go no further than was required to affirm or otherwise rule on the judgment appealed"); *see also Rheox, Inc. v. Entact, Inc*., 276 F.3d 1319, 1324-25 (Fed. Cir. 2002).

V. CLAIMS 1-13 ARE PATENTABLE

Petitioner fails to establish a reasonable likelihood that any claim of the '920 patent is unpatentable under any of the three asserted grounds. Grounds I and II are five- and seven-way obviousness combinations, respectively, that rely on the same primary reference, Cunha (EX 1004). Both are deficient in the same respect: they fail to demonstrate that a person of ordinary skill would have been motivated to increase the dosage of CBD taught by Cunha and would have reasonably expected it to treat partial seizures. Ground III uses a different primary reference, Jones (EX. 1018), but fails to establish that it is prior art to the '920 patent or provide any articulated reasoning or, for that matter, any expert testimony for why a person of ordinary skill would have combined the teachings of Jones with three other references in the ground to arrive at the claims of the '920 patent. Finally, Petitioner fails to present anything other than conclusory arguments for why dependent claims 3-13 would have been obvious, failing even to identify where the prior art teaches most of the additional limitations.

A. A Person of Ordinary Skill Would Not Have Increased the CBD Dosage Taught by Cunha Based on Ames, Bhattacharyya, Lowenstein, and WO '697.

In Ground I, Petitioner fails to show that claims 1-13 of the '920 patent are unpatentable as obvious over Cunha (EX. 1004) in combination with Ames (EX. 1011), Bhattacharyya (EX. 1012), Lowenstein (EX. 1019), and WO '697 (EX. 1020). Petition, p. 34.

Cunha (EX. 1004), the primary reference, does not disclose the claimed dose of CBD to treat partial seizures. The CBD dose that was co-administered with other drugs by Cunha to treat partial seizures, as Petitioner admits, is less than the CBD dose claimed by the '920 patent. *See, e.g.*, Petition, pp. 15-16. Petitioner attempts to compensate for Cunha's failure to teach the dosage recited in the '920 claims—a feature that the prior art characterizes as a "pivotal" consideration with respect to pharmacological effect, *see* Zuardi (EX. 1025), p. 7—by proposing to combine Cunha with four additional references. But none of the references used in Ground I teaches or suggests (1) administering CBD in the dosage claimed by the '920 patent to treat partial seizures, or (2) that increasing the dosage of CBD would have been expected to increase its effectiveness in treating partial seizures.

Multiple review articles in the record discuss Cunha's results and none of them say—or even speculate—that Cunha's results could be improved by increasing the dosage of CBD. Instead, the review articles highlight that even after

Cunha, a great deal of uncertainty remained with respect to the ability of CBD to treat seizures of any type, or even CBD's mechanism of action. *See* EX. 1022 (Pertwee), pp. 24-25 (discussing Cunha's results but then noting that it was not known whether CBD directly causes an anticonvulsant effect, modulates the anticonvulsant effect of other drugs, or both); EX. 1025 (Zuardi), p. 2 (discussing Cunha and Ames' results but then concluding that "the clinical efficacy of CBD on epilepsy is still uncertain"). These review articles confirm that it was not obvious to increase the dose of CBD administered by Cunha to treat partial seizures.

Recognizing Cunha's failure to provide a reason to increase dose, Petitioner is forced to argue that Ames (EX. 1011) suggests increasing the daily amount of CBD to treat seizures. *E.g.,* Petition, p. 42. Ames, however, does not establish that a person of ordinary skill would expect that increasing the dose of CBD taught by Cunha would increase its effectiveness against partial seizures. Indeed, Ames never refers to partial seizures. Instead, Ames says only that CBD was administered to patients "who were institutionalized because of mental retardation and also had frequent seizures which were not controlled on conventional anticonvulsant therapy." EX. 1011, p. 1. Although Ames does not disclose the type of seizures, the prior art taught that seizures accompanying mental retardation were usually associated with generalized, not partial seizures. *See* EX. 1019 (Lowenstein), p. 2 (mental retardation is associated with atypical absence seizures,

not simple partial seizures, complex partial seizures, or secondarily generalized seizures).

Moreover, the CBD treatment administered in Ames did not work. Specifically, Ames found that CBD had no statistically significant effect when administered at a daily 300 mg dose for one week, followed by a daily dose of 200 mg for the next three weeks. EX. 1011, p. 1. Because CBD showed no statistically significant effect, Ames states:

> We decided to increase the dose of CBD because its lack of efficacy might have been due to the fact that the patients were all brain-damaged and severely epileptic.

Id.

Thus, when Ames suggests increasing the dose of CBD, it specifically says to do so because "the patients were all brain-damaged"—a condition known to be associated with general, not partial, seizures. *See* EX. 1019 (Lowenstein), p. 2. Moreover, Ames never actually demonstrated that higher doses of CBD would work for those brain-damaged patients, or what those higher doses would be. Ames never followed through because its supplier of CBD "encountered technical difficulties in procuring the drug." EX. 1011, p. 1. Thus, Ames has only a single speculative statement about a different type of condition. *See Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.,* 655 F.3d 1364, 1376 (Fed. Cir. 2011) (claims nonobvious where prior art's "speculative and tentative disclosure of what 'might'

or 'may' [occur] does not sufficiently direct or instruct one of skill in this art"). Moreover, Zuardi discusses Cunha and Ames together and concludes that "the clinical efficacy of CBD is still uncertain." EX. 1025, p. 2. Ames simply does not suggest to a person of skill that increasing the dose in Cunha would treat partial seizures, as the '920 patent claims. Petitioner fails to identify any teaching in the prior art to increase the dose of CBD in Cunha to treat partial seizures.

Having run out of options, Petitioner can only argue that it would have been a matter of routine optimization to arrive at the claimed dosages. But this argument also fails. *See* Petition, pp. 39 and 55. Petitioner cites two cases to support its argument. The first case is *Pfizer, Inc. v. Apotex*, where the Court held claims unpatentable "because the prior art provided not only the means of creating acid addition salts ***but also predicted the results*****,** which Pfizer merely had to verify through routine testing." 480 F.3d 1348, 1369 (Fed. Cir. 2007) (emphasis added). Here, however, based upon Cunha and Ames, as well as the uncertainty and limited information related to CBD's use for treating seizures, there was no reasonable expectation that increasing Cunha's dosages could treat partial seizures. In contrast to *Pfizer*, the results were unpredictable. In the second case, *In re Peterson*, the prior art disclosed ranges that either fully or at least partially overlapped with the claimed ranges. 315 F.3d 1325, 1327 (Fed. Cir. 2003). However, the present case does not involve overlapping ranges. Thus, *Peterson* is

not relevant. On this record and in view of the complex pharmacological interactions of CBD, Petitioner has failed to show that selecting the CBD dose was routine optimization.

The remaining secondary references that form Ground I (Bhattacharrya, Lowenstein, and WO '697) add nothing to Cunha and Ames.

Petitioner relies on Bhattacharrya (EX. 1012) for the proposition that CBD administered at a dose of 600 mg was well-tolerated in humans and did not produce negative symptoms. Petition, p. 41. However, whether CBD is well-tolerated at a dose of 600 mg does not mean it is efficacious against partial seizures at this dose. In this regard, it is significant that Bhattacharrya did not investigate the ability of CBD to treat partial seizures. Rather, Bhattacharrya studied the effect of CBD on regional brain function during verbal learning—an entirely different application. EX. 1012 (Bhattacharrya), p. 1. Bhattacharrya, therefore, is irrelevant to the fundamental issue of whether it would have been obvious to increase Cunha's 300 mg dose to treat partial seizures.

Petitioner cites Lowenstein for two purposes. First, Petitioner relies on Lowenstein for the proposition that secondary generalized seizures are a type of partial seizure. Petition, pp. 38-39. Second Petitioner relies on Lowenstein for the proposition that there is overlap between drugs used to treat partial seizures and drugs used to treat generalized seizures. *Id.,* pp. 46-47. Neither point is relevant.

Regardless of whether secondary generalized seizures are a type of partial seizure, or whether there are drugs that can treat both partial and generalized seizures, a person of ordinary skill would not have expected, based on Ames' failed trial with severely retarded patients and speculative statement, that increasing Cunha's 300 mg CBD dosage would even treat partial seizures, let alone increase efficacy.

Lastly, Petitioner cites WO '697 (EX. 1020) to show that CBD could be combined with THCV. Petition, p. 50. This feature, however, is found only in dependent claims 3-5 and 10-13. WO '697 does not address the failure of the proposed combination of Cunha and Ames to suggest treating partial seizures with at least 400 mg of CBD, as recited in independent claim 1.

For at least these reasons, Ground I of the Petition fails to demonstrate that Cunha in view of Bhattacharyya, Ames, Lowenstein, and WO '697 renders any claim of the '920 patent obvious.

B. A Person of Ordinary Skill Would Not Have Increased the Dosage of CBD Taught by Cunha Based On Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO '697.

In Ground II, Petitioner fails to show that claims 1-13 of the '920 patent are unpatentable as obvious over Cunha (EX. 1004) in combination with Pertwee (EX. 1022), Malfait (EX. 1023), Lindamood (EX. 1024), Mechoulam (EX. 1021), Zuardi (EX. 1025), and WO '697 (EX. 1020). Petition, pp. 50-51.

Ground II relies on the same primary reference, Cunha (EX. 1004), used for Ground I. As discussed above, Cunha admittedly does not disclose the claimed dose of CBD to treat partial seizures. *See, e.g.*, Petition, pp. 15-16. In Ground II, Petitioner attempts a different approach with a new set of secondary references to compensate for Cunha's failure to teach the dosage recited in the '920 claims. Although it is difficult to determine exactly which secondary references the Petitioner is relying on, Petitioner essentially argues that the secondary references collectively teach that because CBD had a linear dose-response curve for treating seizures, it would have been obvious to increase Cunha's 300 mg/day CBD dose. *See* Petition, pp. 52-59.

Petitioner oversimplifies and mischaracterizes the art, and ignores contradictory data in Pertwee (EX. 1022) regarding CBD doses for treating seizures. A person of ordinary skill would not reasonably expect that increasing the dose of CBD would also increase its ability to treat partial seizures. Contrary to the Petition, it was not well-established that CBD had a linear dose-response curve for treating seizures, let alone partial seizures. Data for CBD's ability to treat seizures was limited, inconclusive, and inconsistent. A person of ordinary skill, based upon the secondary references that Petitioner cites, would have had no reasonable expectation that increasing Cunha's CBD dosage could treat partial seizures.

1. Petitioner cherry picks data from Pertwee to claim that high doses of CBD could treat partial seizures.

Pertwee (EX. 1022) does not teach of person of skill that high doses of CBD would treat partial seizures. Petitioner seizes on a single sentence in Pertwee that refers to two data points in Pertwee's Table 4 involving the MES model of seizures in rats and mice. *See* Petition, pp. 57-59 (quoting Pertwee (EX. 1022), p. 44). From these two studies, Petitioner wrongly argues that a person of ordinary skill "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." Petition, pp. 58-59.

Petitioner cherry-picks those two studies, ignoring numerous other studies disclosed in Pertwee where CBD had no activity in the same model at the same dosage. Petitioner relies on two studies showing that CBD showed activity in the MES model at 12 mg/kg in rats and 80 mg/kg in mice. *See* EX. 1022 (Pertwee), p. 44 and Table 4. The 12 mg/kg study is described in Consroe (EX. 1026) and the 80 mg/kg study is described in Wallace (EX. 1027), both of which the Petition cites. Petition, pp. 57-58. However, Petitioner completely ignores Table 6 of Pertwee, which lists more than a page of results where CBD lacked ***any*** detectable anti-seizure activity at similar doses. *Id.* at 22-23. Table 6 teaches that, in the same MES model, CBD showed no detectable activity in mice at doses of 50-200 mg/kg, 120 mg/kg, and up to 600 mg/kg. *Id.* Table 6 is reproduced below:

Table 6. Models of epilepsy in which CBD lacks detectable activity

Behavioural Model	Test Dose(s) of CBD	Refs.
(1) Seizures induced by passing maximal electroshock currents through corneal electrodes		
Mice not protected from convulsions (hind limb extension)	50 to 200 mg/kg i.g.	125[a]
Duration of hind-limb extensor phase not reduced (mice)	50 to 200 mg/kg i.g.	125[a]
No elevation of 60 Hz-electroshock threshold for inducing a minimal seizure (front limb and jaw clonus) (mice)	120 mg/kg i.p. 120 mg/kg i.p. up to 600 mg/kg i.p	110 107[b] 100
(2) Seizures induced by pentylenetetrazol		
No elevation of threshold dose for inducing minimal seizures (clonic convulsions) (rats)	34 mg/kg p.o. 17 mg/kg i.v.	127
No elevation of threshold dose for inducing minimal seizures (clonic convulsions/front limb and jaw clonus) (mice)	120 mg/kg i.p. 150 mg/kg i.g.	110[b] 125[b]
Number of mice with clonic convulsions not reduced	45 mg/kg i.v. 200 to 400 mg/kg i.p.	109 95
Onset of tonic seizures not delayed significantly (mice)	10 mg/kg i.v.	112
(3) Seizures induced by other convulsant agents		
No attenuation of tonic or tonic-clonic convulsions induced by handling plus Δ^9-THC (mice)	40 mg/kg i.p.	128[b]
No protection from hind limb extension/tonus induced by strychnine	400 mg/kg i.p.	95
Little or no protection from clonus induced by: 3-mercaptopropionic acid (little protection) picrotoxin (no protection) isonicotinic acid hydrazine (little protection) bicuculline (little protection) strychnine (little protection)	50 to 200 mg/kg i.p. 100 to 300 mg/kg i.p. 200 to 400 mg/kg i.p. 300 to 600 mg/kg i.p. 400 mg/kg i.p.	95
Onset of picrotoxin-induced clonic and tonic seizures and of strychnine-induced tonic seizures not delayed (mice)	10 mg/kg i.v.	112
(4) Photically-evoked cortical afterdischarge potentials in unanaesthetized rats		
Number of after discharge potentials not reduced	50 mg/kg i.p.	130[b]
"Total excursion" of the sum of afterdischarge potentials evoked by 50 photic stimuli unaffected	50 mg/kg i.p.	130[b]
(5) Spontaneous activity of hippocampal CA1 cells in unanaesthetized rats		
Spontaneous activity unaffected	10 mg/kg i.p.	129
(6) Seizure activity in cobalt-epileptic rats		
No effect on the frequency of focal epileptic potentials induced in the parietal cortex of unanaesthetized rats by cobalt wire positioned on the dura for up to 19 days	1 to 200 mg/kg i.p.	94[b]
No effect on tonic and clonic movements of front limbs and facial muscles or on EEG activity in frontal and parietal cortices of unanaesthetized rats with cobalt wires bilaterally inserted into the cerebral cortex for up to 12 days	60 mg/kg i.p. twice daily	126

Table 6. Continued

Behavioural Model	Test Dose(s) of CBD	Refs.
(7) Seizure activity in iron-epileptic rats		
No effect on the amplitude of focal epileptic potentials that developed in the parietal cortex of unanaesthetized rats after injection of ferric chloride into the cortex	1 to 100 mg/kg i.p.	121
(8) Kindled afterdischarges induced by repetitive stimulation through electrodes positioned in the left subiculum of unanaesthetized rats		
No effect on afterdischarge (seizure) spread from subiculum to dorsal hippocampus and frontal cortex	0.3 to 3 mg/kg i.p.	111[b]

[a]CBD and phenytoin behaved differently in this investigation.
[b]CBD and phenytoin behaved similarly in this investigation.

It is only through hindsight that Petitioner selects the two studies in Table 4 at the expense of the contradictory studies in Table 6, and then proceeds through a series of calculations, conversions, and assumptions to arrive at the claimed dosage. *See* Petition, pp. 57-59, relying on Mechoulam (EX. 1021), Malfait (EX. 1023), and Lindamood (EX. 1024). The hindsight nature of Petitioner's argument is confirmed by the rest of Pertwee, which repeatedly highlights that CBD had an unknown clinical profile. *See, e.g.*, EX. 1022 (Pertwee) at 44 ("it will be important to determine how the clinical profile of CBD differs from the profiles of established medicines ….").

Pertwee actually describes Cunha's results and never makes the same unsupported leap of faith that Petitioner does. *See id.* at 24-25. Instead of suggesting increasing Cunha's dose, Pertwee highlights that it is not even clear after Cunha whether CBD induces a "direct anticonvulsant effect" or instead "modulate[s] the anticonvulsant effects of some of these other drugs as is indeed it has been observed to do in animal experiments (see above)." *Id.* Pertwee ***does not*** say that the two studies in Table 4, conveniently chosen by Petitioner, should be credited instead of the contradictory studies in Table 6. The contemporaneous statements in Pertwee show that a person of skill would not—and did not—draw the conclusions urged by Petitioner.

Petitioner's methodology is flawed as a matter of law. Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc*., 159 F.3d 534, 546 (Fed. Cir. 1998). The Board should reject the Petitioner's hindsight-based conclusion.

2. Other animal models of seizure suggested that CBD might have a bell-shaped dose-response curve for partial seizure.

Before the '920 patent's filing date, the scientific literature suggested that CBD's dose-response curve for partial seizure may well have been bell-shaped. *See* EX. 2003 (Turkanis), p. 8; EX. 1025 (Zuardi), p. 7. Nonetheless, Petitioner and its expert, Dr. Benet, baldly assert that it was well-established before the '920

patent's filing date that CBD had a linear dose-response curve for treating partial seizures. *See* Petition, pp. 55-56; EX. 1003 (Benet Decln), ¶ 22 ("the literature has clearly shown that, prior to the filing date of the '920 patent, CBD was shown to have a conventional dose response curve where drug response increased with dose in a monophasic fashion."). In fact, the literature suggested that increasing the dose of CBD might ***decrease*** its ability to treat partial seizures. For example, Turkanis reported results from the limbic seizure model, an animal model closely associated with complex partial seizures, that suggested CBD's ability to treat partial seizures might have a bell-shaped curve. *See* EX. 2003 (Turkanis), pp. 8 and 10 ("The limbic system, however, is considered to be closely associated with complex partial seizures"). According to Turkanis, CBD displayed "significant" results in the limbic seizure model "at low doses … but not at high doses." *Id.* at p. 8. Thus, Turkanis teaches that increasing the dose of CBD could ***decrease*** its effect against partial seizures.

As Turkanis explains, it was not surprising that CBD's effect against partial seizures could be worse at higher doses because cannabinoids were known "to cause qualitatively different responses as a function of dose." *Id.* No fewer than three other pharmacological effects of CBD were known to display a bell-shaped curve: (1) the anti-anxiety effect, *see* EX. 2004 (Guimaraes), p. 1 and Fig. 2; (2) the anti-inflammatory effect, *see* EX. 1023 (Malfait), p. 4 ("both the lowest dose

… and the highest dose … were inactive"); and (3) the neuroprotective effect, *see* EX. 2005 (Braida), Figure 3.

Petitioner and its declarant, Dr. Benet, ignore this body of literature. Instead of acknowledging Turkanis or grappling with the known complexity of CBD's pharmacology, Dr. Benet selects data from a single type of animal model, the maximal electroshock (MES) model, to argue that the literature "clearly" showed that CBD had a conventional dose-response curve. *E.g.,* EX. 1003 (Benet Decln), ¶ 22. The MES model, however, is a model of ***generalized*** seizures. *See* EX. 1028 (Castel-Branco), p. 1. (the MES model was used to "predict[] drugs effective against generalized seizures of the tonic-clonic (grand mal) type"); *see also* EX. 2001 (Mares), p. 1 ("Maximal electroshock seizures (MESs) are a model of generalized tonic-clonic seizures."). Castel-Branco states that the MES model was known to be a flawed model for partial seizures. *See* EX. 1028 (Castel-Branco), p. 5 ("the MES test can fail to identify drugs that are clinically effective in treating partial seizures").

Dr. Benet makes the unsupported assertion that the MES model "is the best model" for ***all*** partial seizures. EX. 1003 (Benet Decln), ¶ 17. Dr. Benet cites nothing to support that claim. Although Dr. Benet discusses Castel-Blanco (EX. 1028), see EX. 1003 (Benet Decln), ¶ 16, he omits the teachings in Castel-Branco that the MES model was a flawed model for partial seizures.

Dr. Benet relies only on his own experience and background to support his claim regarding the MES model. Nothing in his declaration or CV, however, suggests that Dr. Benet has any substantial experience with animal models of epilepsy or CBD. None of his cited publications involve animal models of seizure or CBD. None of the paragraphs detailing his Education and Professional Background describe experience with animal models of epilepsy or CBD.

Petitioner did submit a declaration from someone with experience related to epilepsy. That person, Dr. Marson, ***did not*** testify that the MES model would have been the "best" model for all partial seizures. *See* EX. 1002 (Marson Decln). Thus, to support its claim that the MES model was the "best" model for partial seizures, Petitioner relies only on the unsupported testimony of one of its two declarants—the one without any substantial experience with CBD or epilepsy. *See Rhone-Poulenc Agro, S.A. v. DeKalb Genetics Corp.,* 272 F.3d 1335, 1358 (Fed. Cir. 2001) ("In an obviousness determination, some evidentiary support must be offered beyond an expert's conclusory opinion.").

3. A person of ordinary skill would not reasonably expect that increasing Cunha's CBD dosage would treat partial seizures.

Petitioner fails to show that a person of ordinary skill would have been motivated to increase Cunha's 300 mg/day dose of CBD to treat partial seizures or have a reasonable expectation of success that increased doses could treat partial seizures.

Petitioner ignores the complex pharmacology of CBD and how little was known about its ability to treat seizures of any kind before the '920 patent's filing date. Petitioner fails to identify any supportable reason why a person of ordinary skill would discard the results from the limbic seizure model suggesting a bell-shaped dose-response curve for partial seizures and choose to believe that CBD displayed a conventional linear dose response based only on data from the MES model. Even if the MES model were applicable to partial seizures, Petitioner ignores the fact that the MES model data was contradictory and inconclusive. *Compare* EX. 1022 (Pertwee), Table 4, pp. 19-20 ("Behavioural models of epilepsy in which CBD shows activity") with Table 6, pp. 22-23 ("Models of epilepsy in which CBD lacks detectable activity").

Ground II of the Petition, just as Ground I, fails to demonstrate that that Cunha in view of Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO '697 renders any claim of the '920 patent obvious.[2]

[2] Petitioner relies on Zuardi (EX. 1025) to show that high doses of CBD are safe. *See* Petition, p. 59. However, as discussed in the context of Ground I, safety is not the same as efficacy. Moreover, as in the case of Ground I, Petitioner relies on WO '697 only for dependent claims 3-5 and 10-13, which require administering THCV with CBD. *Id.,* p. 60. WO '697 does not cure the deficiencies of the other six references in the proposed obviousness combination.

C. Claims 1-13 Would Not Have Been Obvious Over Jones in view of Cunha, Lowenstein, and WO 2009/007697.

The Board should also reject Ground III of the Petition, which relies on a new primary reference, Jones (EX. 1018). Petitioner fails to establish that Jones is prior art to the '920 patent. Independently, Petitioner fails to offer a reasoned explanation as to why a skilled artisan would have selected the teachings of Jones and combined them with the three additional references to achieve the claimed invention, while reasonably expecting the four-way combination to treat partial seizures. Neither of the declarations that Petitioner submitted discusses Jones or this ground at all. Accordingly, for either of two reasons, Petitioner has not demonstrated that there is a reasonable likelihood that any of the challenged claims is unpatentable on this ground.

1. Petitioner fails to establish that Jones is prior art.

The only evidence of record as to when Jones was published is the 2010 copyright on the first page of the article. *See* EX. 1018 (Jones), p. 1. Petitioner acknowledges that the '920 patent is entitled to a priority date of no later than June 29, 2010. *See* Petition, p. 27. Thus, even if Jones were published ***sometime*** in 2010, that fact alone does not establish that it was published ***before*** June 29, 2010 and, therefore, should be considered prior art under 35 U.S.C. § 102(a).

Recognizing that the 2010 copyright cannot reasonably establish that Jones is prior art, Petitioner asserts with no supporting evidence that Jones had an "e-

publication date of November 11, 2009." *See* Petition, p. 61. Jones does say that it was "accepted" on November 9, 2009, but nowhere does it say that it was published, electronically or otherwise, anytime in 2009. *See* EX. 1018 (Jones), p. 1. Accordingly, Petitioner presents no evidence to meet its burden that Jones is prior art to the '920 patent. *See ServiceNow, Inc. v. Hewlett-Packard Company*, IPR2015-00716, slip op. at 8 (PTAB Aug, 26, 2015) (Paper No. 13) ("Petitioner has the burden to establish in its Petition a reasonable likelihood of success, including … making a threshold showing that the [asserted references] are 'printed publications' within the meaning of 35 U.S.C. §§ 102[a] and 311(b)."") (citing 35 U.S.C. § 314(a); 37 C.F.R. § 42.108(c)).

2. Petitioner provides no reasoned explanation to support its proposed combination of Jones and various secondary references.

Ground III has a second and independent deficiency: neither the Petition nor the Petitioner's declarants identify why a person of ordinary skill would have selected Jones, combined it with three other references, and reasonably expected the resulting four-way combination to treat partial seizures. *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012) ("a party seeking to invalidate a patent as obvious must demonstrate … that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the

skilled artisan would have had a reasonable expectation of success from doing so.") (internal quotation omitted).

Petitioner presents only cursory attorney argument for Ground III, an argument that neither of Petitioner's declarants supports or even addresses. Petitioner does not even identify the claimed dosage limitation (*i.e.*, a daily dose of CBD of at least 400 mg) in the prior art, but instead baldly asserts that "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." Petition, p. 63. Thus, Petitioner resorts to arguing, in a conclusory manner, that a person of ordinary skill starting with Jones ***would have*** arrived at this claim limitation—which is nowhere in the prior art—but never presents any testimony from someone who qualifies as a person of ordinary skill to corroborate that supposed journey.

Where the technology at issue is complex, expert testimony is essential. *See Alexsam, Inc. v. IDT Corp*., 715 F.3d 1336, 1347 (Fed. Cir. 2013) ("expert testimony regarding matters beyond the comprehension of laypersons is sometimes essential, particularly in cases involving complex technology.") (internal quotation omitted); *see also Proveris Sci. Corp. v. Innovasystems, Inc.,* 536 F.3d 1256, 1267 (Fed. Cir. 2008) (affirming the district court's requirement of expert testimony to prove invalidity where "th[e] subject matter [wa]s sufficiently complex to fall

beyond the grasp of an ordinary layperson"). Underscoring the complexity of the claimed technology, Petitioner believed it was necessary to introduce ***two*** extensive declarations for Grounds I and II. *See Alexsam,* 715 F.3d at 1347 ("The claim that the technology is simple is belied by the fact that both sides believed it necessary to introduce extensive expert testimony regarding the content of the prior art.").

Because Petitioner fails to provide a reasoned explanation for obviousness under Ground III, supported by expert testimony, Petitioner fails to establish a reasonable likelihood that claims 1-13 would have been obvious based upon the four-way combination of references set forth in Ground III. *See Alexsam*, 715 F.3d at 1348 (affirming finding of nonobviousness, because "[e]xpert testimony was required not only to explain what the prior-art references disclosed, but also to show that a person skilled in the art would have been motivated to combine them in order to achieve the claimed invention.).

D. Petitioner Fails to Identify Where to Find Limitations from Dependent Claims 3-13 in the Prior Art, Much Less Offer a Reasoned Explanation for Why They Would Have Been Obvious.

All three grounds in the Petition are deficient with respect to dependent claims 3-13. Petitioner fails to locate most of those added limitations in the prior art, let alone provide a reasoned explanation for a skilled artisan would have selected those limitations while having a reasonable expectation of success. Petitioner also presents no expert testimony in support of its cursory argument that

the dependent claims would have been obvious. Instead, for most of the dependent claims, Petitioner errs by arguing that the dependent claim would have been obvious "for the same reasons" as claim 1, without identifying or analyzing the claim's additional limitations. What suffices to render one claim obvious, however, does not necessarily suffice for a dependent claims containing additional elements. *See, e.g.,* 35 U.S.C. § 282 ("Each claim of a patent ... shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim."); *see also Altoona Publix Theatres v. American Tri-Ergon Corp*., 294 U.S. 477, 487 (1935) ("[E]ach claim must stand or fall, as itself sufficiently defining invention, independently of the others").

Claims 3-5. These claims require that CBD be administered in combination with tetrahydrocannabivarin (THCV) (claim 3) and further require that the THCV be administered in a daily dose of at least 1.5 mg (claim 4) or 15 mg (claim 5). Petitioner presents no testimony from either of its experts as to claims with these additional limitations would have been obvious. Instead, Petitioner relies only on cursory references to WO '697 (EX. 1020), which teaches a pharmaceutical formulation "preferably" comprising CBD and THCV. *See id.* at Abstract. Nowhere, however, does WO '697 teach administering its pharmaceutical formulation to treat partial seizures. WO '697 says only that:

> Examples of diseases and conditions that are the result of the background tone of constitutively active cannabinoid receptors include but are not limited to obesity, schizophrenia, epilepsy, cognitive disorders such as Alzheimer's disease, bone disorders such as 20 osteoporosis, bulimia, obesity associated with type II diabetes (non-insulin dependent diabetes), the treatment of drug, alcohol and nicotine abuse or dependency and inflammatory disorders.

Id. a p. 3, ll. 15-23; *see also* p. 10, ll. 21-30.

It is undisputed that epilepsy is grouped in two basic categories: partial and generalized. EX. 1008 (McCormick), p. 1; EX. 1001, 2:35-36; *see also* Petition, pp. 8-9. Petitioner offers no explanation for why a person of ordinary skill would interpret WO '697 as teaching that the combination of CBD and THCV could be used to treat ***partial seizures*** instead of some other form of epilepsy.

Worse still, Petitioner fails to identify where the prior art teaches the dosages of THCV recited in dependent claims 4 and 5. Petitioner simply repeats three times that "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." Petition, pp. 50, 60, and 64.

For at least these reasons, Petitioner has not demonstrated that there is a reasonable likelihood that claims 3-5 are unpatentable. *See ActiveVideo Networks,*

Inc. v. Verizon Comms., Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012) (claims not proven obvious where challenging party's "failed to explain how specific references could be combined, which combination(s) of elements in specific references would yield a predictable result, or how any specific combination would operate or read on the asserted claims").

Claims 6-8. These claims depend from claim 1 and further require that the CBD is present as a plant extract (claim 6) and that the plant extract have an amount of THC less than 5% (claim 7) or 1% (claim 8) by weight. To argue that these claims are obvious, Petitioner says only: "All of these limitations are obvious to a person of ordinary skill in the art for all the same reasons stated above." Petition, pp. 49, 59, and 65. Just as with claims 3-5, Petitioner fails to identify where the prior art teaches these limitations or offer a reasoned explanation for why a person of ordinary skill would have considered these limitations desirable. Accordingly, for at least these reasons Petitioner has not demonstrated that there is a reasonable likelihood that claims 6-8 are unpatentable.

Claims 10-12. These claims depend from claim 3 and require both that the CBD be administered with THCV and that it is present as a plant extract. Moreover, claims 11 and 12 limit the amount of THCV that is present in the plant extract. Effectively, these claims combine the limitation from claim 3 with the limitations from claims 6-9. Just as with those claims, Petitioner has not

demonstrated that there is a reasonable likelihood that claims 10-12 are unpatentable.

Claims 9 and 13. These claims require that CBD is present as a pure or isolated cannabinoid. Petitioner presents no additional analysis for this limitation, other than that it should be assumed to be obvious "for the same reasons" as claim 1. Petitioner includes no expert testimony to prove that this claim would have been obvious and fails to identify where the prior art teaches this limitation. Accordingly, for at least these reasons, Petitioner has not demonstrated that there is a reasonable likelihood that claims 9 and 13 are unpatentable.

VI. CONCLUSION

For at least the foregoing reasons, Patent Owners request that the Board deny the Petition. Petitioner has failed to demonstrate a reasonable likelihood that any of the challenged claims are unpatentable.

Please apply any fees or any credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date:/April 11, 2017/

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CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owners' Preliminary Response totals 8,299, which is less than the 14,000 allowed under 37 CFR § 42.24(b)(1).

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on April 11, 2017, a complete and entire copy of this Patent Owners' Preliminary Response and supporting exhibits were provided via electronic service, to the Petitioner by serving the correspondence address of record as follows:

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