IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Merial, Inc., Petitioner

v.

Sergeant's Pet Care Products, Inc.
Patent Owner

U.S. Patent No. 8,614,244 to Larry Nouvel
Issue Date: December 24, 2013
Title: Spot-on Pesticide Composition

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Inter Partes Review No.: IPR2016-_____

Petition for *Inter Partes* Review of U.S. Patent No. 8,614,244
Under 35 USC §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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I. INTRODUCTION

Merial Inc. ("Petitioner") respectfully petitions for *Inter Partes* Review, seeking cancellation of Claims 1-22 (the "challenged claims") of U.S. Patent No. 8,614,244 to Nouvel ("the '244 patent") (EX1001). Based on the records of the USPTO, the '244 patent is assigned to Sergeant's Pet Care Products, Inc. ("Sergeant's" or "the patent owner").

II. OVERVIEW

The claims of the '244 patent are unpatentable; they failing to satisfy the nonobviousness requirements of 35 USC § 103 based on a combination of the relevant prior art in view of the knowledge of a person of ordinary skill in the art ("POSA"). [1] The claims of the '244 patent are directed to methods of combating common animal ectoparasites, *e.g.*, fleas and ticks, using a spot-on composition by using a combination of two known parasiticides: fipronil and cyphenothrin.

[1] As to the '244 patent, the POSA would have been highly educated to a level such as a doctorate in veterinary medicine (D.V.M.) or a Ph.D. in parasitology with at least several years of experience in topical veterinary formulations. The POSA would have either personally possessed, or had access to, knowledge and skills from clinical research veterinarians and pharmaceutical formulation scientists. (EX1002¶30).

The ability of fipronil and cyphenothrin to kill common animal pests has been known for decades. (EX1002; Declaration of Dr. Jeffrey N. Clark, D.V.M., Ph.D.; ¶¶52-54 and 57). The alleged "invention" involved nothing more than taking a prior art spot-on composition of fipronil and cyphenothrin, and through routine experimentation developing a low concentration composition having predictable properties. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id*.).

In this regard, the patent owner admitted that fipronil "was known to work well with cyphenothrin." (EX1003, p. 231, patent owner's Response dated May 15, 2013, Declaration of inventor Larry Nouvel dated May 15, 2103 (hereinafter "Nouvel Declaration I" at ¶10). This is because of the complementary mechanisms of action of each agent. (EX1002, ¶58). Namely, cyphenothrin is known to be fast acting, whereas fipronil was known to have relatively longer-lasting efficacy. (*Id*. at ¶¶54, 57 and 58). Prior art reference WO 2008/080542 (EX1004; "the '542 publication," a German-language reference for which an English-language translation with certification is submitted as EX1005) teaches a spot-on composition comprising an N-arylpyrazole active agent, such as fipronil in combination with an α-cyanopyrethroid active agent (a class the art recognizes includes cyphenothrin) for controlling ectoparasites on animals. (EX1005, p. 1,

¶0001).

Other prior art discloses the efficaciousness of low concentrations, i.e., less than 20% (w/w), of α-cyanopyrethroids, specifically cyphenothrin.[2] For example, U.S. Patent No. 4,902,510 (EX1006; "the '510 patent") teaches the topical use of a pyrethroid on an animal at "a concentration of 10 to 30 kg/m^3, most advantageously 15 kg/m^3", which corresponds to 1.5% (w/v)[3] (EX1002, p. 32, n.5, showing the conversion of kg/m^3 to % (w/v)), to combat ticks, etc. (EX1006 at 2:45-47). Indeed, the '510 patent teaches Examples 1-6, in which an α-cyanopyrethroid (alphacypermethrin) was administered at the very low dose of 0.3 g per 100 kg animal body weight (*Id.*, at 6:57-60), and exhibited an "overall tick control" of *94.5% or better* efficacy against adult ticks over 21 days. (*Id.*, at 6-7, Table III). Therefore, a POSA would have expected that α-cyanopyrethroids, such as cyphenothrin, would be highly efficacious for several weeks at low concentrations.

In addition to the complementary action of fipronil and cyphenothrin mentioned above, the art provides motivation for a POSA to use as low an amount

[2] Cyphenothrin is recited within a limited list of only 11 α-cyanopyrethroids.

[3] As Dr. Clark opines, there is typically a very close correlation between % (w/v) and % (w/w) in spot-on compositions. (EX1002, ¶69).

of cyphenothrin in a spot-on formulation as possible for at least two reasons. First, a POSA wishes to use as little active agent as possible because all active agents have side effects. Second, at the relevant date, it was known that high concentrations of cyphenothrin caused a detrimental skin condition known as paresthesia. (EX1002, ¶55). Additionally, when combining cyphenothrin with fipronil, a POSA would have expected a lower concentration of cyphenothrin, such as that used in the prior art, could be used without any loss of efficacy because of the activity fipronil contributes to the activity of the combination product. (*Id*., ¶89). This is because the mechanisms of action of cyphenothrin ("quick-kill") and fipronil (relatively slower-acting, and relatively longer-lasting efficacy) complement each other, and, as a result, a POSA would have expected the combination to have at least an additive effect of the two active agents. (*Id*.). That is, because of the additive effect, there would have been a reasonable expectation of success that a low concentration of cyphenothrin in combination with fipronil would have high efficacy (>90%) for at least 30 days.

For example, it was known to a POSA that one could apply an effective dosage of a composition comprising lower amounts of cyphenothrin to an animal and still have excellent activity against fleas for at least 23 days and ticks for 30 days. The Environmental Protection Agency (EPA) Product Performance and Efficacy Report (EX1007; "EPA Report") for patent owner's Cyphenothrin

Squeeze-On™ product demonstrated that one could reduce the dose of cyphenothrin from 50 mg/kg to 25 mg/kg (a dosage that falls squarely within the recited range in claim 9 of the '244 patent), and still maintain greater than 90% efficacy against fleas for up to 23 days and greater than 90% efficacy against the brown dog tick for up to 30 days. (EX1007, p. 3/31 under "MRID 46166110"). And this level of activity is for a cyphenothrin-only composition, i.e., even in the absence of fipronil and the additive effect discussed above.

During prosecution, the patent owner also alleged incorrectly that a level of 25 mg/kg cyphenothrin would not work beyond 21 days due to the low dosage and alleged instability of the molecule. (EX1003, p. 160, patent owner's Response dated May 15, 2013, at p. 13, second paragraph, penultimate sentence). This assertion was made though the patent owner was very much aware of its own data submitted to the EPA, not disclosed to the U.S.P.T.O, that show 25 mg/kg has >90% efficacy against ticks for up to 30 days. (EX1007, p. 3/31 under "MRID 46166110"). Also during prosecution, the patent owner incorrectly alleged that "of all the pyrethroids, cyphenothrin is the least stable." (EX1003, patent owner's Response dated October 1, 2013, p. 11, third paragraph, second sentence). This argument is meritless at least because the PTAB has rejected similar instability arguments. *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829 (Fed. Cir. 2015). Further, as explained by Dr. Clark, cyphenothrin was known in the art to be an α-

cyanopyrethroid, which is a class of pyrethroids developed to be the most potent and longest-acting type of pyrethroids. (EX1002, ¶52).

The patent owner's misstatements did not end there. During prosecution, the patent owner took liberties when alleging that the teachings of the '542 publication and several pieces of art "teach away" from lower concentrations of cyphenothrin. (EX1003, pp. 083-085, patent owner's Response dated October 1, 2013, at pp. 11-13). While the '542 publication reference may mention preferred higher amounts of Type I pyrethroids, it also teaches preferred lower amounts of α-cyanopyrethroids that a POSA would reasonably believe would work, particularly in light of the other prior art. (EX1002, ¶65). Hence, as set forth below, the claims of the '244 patent are not inventive in any way and are invalid as obvious as matter of law.

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

A. Each Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest is Merial Inc.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters Involving the '244 patent

To Petitioner's knowledge, there are no judicial matters to report.

2. Administrative Matters

The Public Patent Application Information Retrieval ("Public PAIR")

system indicates the '244 patent issued on December 24, 2013, and claims priority to U.S. Provisional Patent Application Nos. 61/297,154, filed January 21, 2010; and 61/244,788, filed September 22, 2009. Public PAIR further indicates the presence of other related patents and family members. (EX1008).

C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), 42.10(a), and 42.10(b):

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IV. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a)) AND

PROCEDURAL STATEMENTS

Petitioner certifies that (1) the '244 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '244 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(c), respectively. The required fee is paid when filing the Petition, and the Office is authorized to charge any fee deficiencies and credit overpayments, to Deposit Acct. No. 22-0259 (Customer ID No. 99562).

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

IPR of Claims 1-22 of the '244 patent is requested on the following grounds:

1. Claims 1-7 & 10-22 under 35 USC §103 over WO2008/080542, in light of U.S. Patent No. 4,902,510; and
2. Claims 8 & 9 under 35 USC §103 over WO2008/080542, in light of U.S. Patent No. 4,902,510 in further light of EPA 2006 Product Performance/Efficacy Review.

Pursuant to 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds, this Petition includes a Declaration of technical expert, Dr. Jeffrey Clark, (EX1002), explaining what the POSA would have understood, based on common, general knowledge in this field and the available 102(b) prior art as of the critical date of the '244 patent, i.e., September

21, 2008. Dr. Clark is an expert in the field of veterinary medicine and veterinary pharmaceutical formulations, particularly, formulations for topical administration.

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

Petitioner requests IPR and cancellation of claims 1-22 of the '244 patent. The following detailed analysis sets forth the reasons for the relief requested.

VII. THE '244 PATENT

Generally speaking, the challenged claims of the '244 patent are directed to methods of killing common pests on animals comprising localized ("spot on") applications of fipronil and cyphenothrin at various concentrations. There are five independent claims (claims 1, 10, 16, 19 and 20). The text of claim 1 is reproduced below:

> 1. A method of killing insect and pest pupae and adults on an animal, which method comprises administering a localized cutaneous application between the shoulders of the animal, a spot-on composition comprising 8% to 11% (w/w) fipronil, 3% to 16% (w/w) cyphenothrin, and 60% to 80% (w/w) organic solvent.

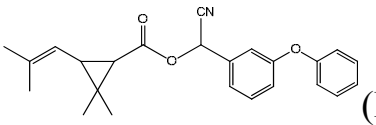
The remaining independent claims are similar to claim 1, other than changing amounts of the recited elements, or adding other common components such as antioxidants (e.g, claim 10), S-methoprene (claim 16), pyriproxyfen (claim 19), or diethylene glycol monoethyl ether (claim 20). Regardless, all of these claims and the resulting dependent claims would have been obvious to a POSA.

A. Claim Construction

The challenged claims must be given their broadest reasonable interpretation in light of the specification of the '413 patent. *See* 37 C.F.R. § 42.100(b). Under this standard, no terms or phrases require specific construction.

B. State of the Art

1. Cyphenothrin

Cyphenothrin was a known as an effective parasiticide having this structural formula  (EX1002, ¶50). Cyphenothrin is referred to as an α-cyanopyrethroid pyrethroid because it possesses a cyano group ("-CN") in the alpha-position relative to the ester group (*Id*.). Additionally, cyphenothrin, like all pyrethroids, can be classified based on the symptomology it produces in insects and mammals. (*Id*., ¶51). Because cyphenothrin produces Type II symptoms as well as Type I symptoms, it is also referred to as a Type I/II pyrethroid. (*Id*.).

The α-cyanopyrethroid class of pesticides (which includes cyphenothrin) was developed to improve upon the natural pyrethrin compounds in terms of activity and photostability. (*Id*., ¶51). First-generation pyrethroids, such as allethrin, were developed in the 1940s, and while the compounds developed in the 1950s improved upon their natural analogs they did not possess sufficient environmental stability. In the 1960s, the second-generation of pyrethroids were

introduced and were being marketed as providing improved killing efficacy and photostability. (*Id*.). By 1972, the third-generation of pyrethroids was introduced. These pesticides, again, possessed higher activity and photostability than the previous generations. (*Id*.).

The fourth-generation of pyrethroids, which included the α-cyano compounds, were known prior to September 2008. (*Id*.). Fourth-generation of pyrethroids are considered the most potent and longest-lasting of the pyrethroids, and this remains true even today. (*Id*.). Cyphenothrin is a fourth generation pyrethroid, and has been used in a commercial spot-on product prior to the critical date. (*Id*., ¶53). This spot-on composition was known in the art and taught to be useful against ectoparasites, e.g., fleas and ticks, after topical administration on dogs. (*Id*.).

In particular, by September 2008, a POSA would have known that α-cyanopyrethroids provide a "quick-kill" on arthropods because of their mechanism of action. (*Id*., ¶54). Said another way, within just a few hours after exposure, α-cyanopyrethroids kill the flea or tick on the animal. (*Id*.). It is common sense that the α-cyanopyrethroid's fast speed of kill would have made them desirable for topical products because of the fast relief to the animal (and its owner) from distressful infestations by fleas and ticks. (*Id*.).

However, the art recognized that high concentrations administration of

cyphenothrin had associated toxicity problems. Indeed, the prior art disclosed that cyphenothrin caused skin irritation. (*Id*., ¶55). The condition is known as paresthesia and was tied to the administration of high concentration topical cyphenothrin. (*Id*.). Moreover, dogs have become sick after topical application of high concentration cyphenothrin (i.e., levels of 50 mg/kg using the patent owner's registered 40% cyphenothrin spot-on product). (*Id*., ¶56). Though cyphenothrin provides excellent beneficial properties, given the noted problems of high concentration cyphenothrin in spot-on products, a POSA would have been motivated to reduce the amount of cyphenothrin.

2. Fipronil

As of September 2008, a POSA was well aware that fipronil is a highly effective and long-lasting ectoparasiticide.[4] (*Id*., ¶57). As of the critical date, fipronil was known to be especially well-suited for topical administration in a spot-on composition.[5] (*Id*.). Ticks and fleas that contact fipronil on the skin and hair of the animal would die without ever having to take a blood meal from the animal.

[4] The term "ectoparasites" refers to a pest that is present on the skin of an animal, such as fleas and ticks. An endoparasite is an internal parasite.

[5] Spot-on compositions contain a small volume of liquid that is administered as a single spot on the back of an animal. (EX1002, ¶59).

(*Id*.). In fact, fipronil-containing products are among the most successful anti-parasitic products in the animal health field. (*Id*.). Indeed, fipronil is the active ingredient in topical spot-on products, e.g., Frontline® Top Spot, which has been on the market since before the critical date of the '244 patent. (*Id*.). It was known that the fipronil-containing spot-on products, such as Frontline® Top Spot, were effective for at least one month against ticks and at least 3 weeks against ticks. (EX1010).

3. Cyphenothrin and Fipronil Complement Each Other

As discussed above, fipronil and cyphenothrin act through different mechanisms. Cyphenothrin provides a "quick-kill" fast-acting property, while fipronil provides a slower-acting, yet highly efficacious property. (*Id*., ¶58). As such, these two mechanisms complement each other. That is, in combining the two, a POSA would take advantage of different mechanisms of action whereby, together, each of cyphenothrin and fipronil provides a property the other does not possess. (*Id*.). For at least this reason, a POSA would have been motivated to combine the different, complementary properties of fipronil and cyphenothrin. (*Id*.).

C. Ground 1: Claims 1-7 and 10-22 Would Have Been Obvious In Light of the '542 Publication and the '510 Patent

1. Scope and Content of the Relevant Prior Art

a) The '542 Publication

The '542 publication (EX1004, the English translation with certification is

submitted herewith as EX1005) published on July 10, 2008, and is 102(b) prior art. The ’542 publication teaches spot-on topical formulations that can contain the combination of an α-cyanopyrethroid, such as cyphenothrin, and fipronil. (EX1002, ¶60). The U.S. counterpart of the ’542 publication, U.S. Patent Pub. Appl. No. 2010/0016398, was applied by the Examiner under § 103 to reject the claims as obvious.[6]

Specifically, the ’542 publication teaches a spot-on formulation that can contain an α-cyanopyrethroid (e.g., cyphenothrin) and a N-arylpyrazole (e.g., fipronil) for use in controlling pests, *e.g*., ticks and fleas, on animals, such as, dogs and cats. “The invention relates to novel compositions for controlling parasites on animals, comprising an N-arylpryazole and a pyrethroid . . . .” (EX1005, p. 1, ¶0001; *see also*, ¶0003 discussing fipronil products). With regard to the amount of an α-cyanopyrethroid, the ’542 publication states:

> For the compositions, the combination partners of the N-arylpyrazoles are preferably arthropodicidal pyrethroids, in particular of the cyanopyrethroid (for example flumethrin), type-1 pyrethroid (for example permethrin) or non-ester pyrethroid (etofenprox) type.

[6] Not all of the prior art references discussed in this petition were disclosed to the Examiner, and the Examiner could not have considered the arguments discussed herein.

> Here, α-cyanopyrethroids (for example alpha-cypermethrin, cyfluthrin, beta-cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, flucythrinate, flumethrin, tau-fluvalinate) are preferably employed in a concentration range of from 0.01 to 5% by weight, and a synergist is added, if appropriate (as described, for example, in WO 04/098290). Particular preference is given to using cypermethrin, cyfluthrin, deltamethrin and flumethrin in a concentration range of from 0.025 to 0.25% by weight. Very particular preference is given to using flumethrin in a concentration range of from 0.05 to 1.25% by weight.
>
> Type-1 pyrethroids (for example allethrin, bioallethrin, permethrin, phenothrin, resmethrin, tetramethrin, transfluthrin) are preferably employed in a concentration range of from 20 to 70% by weight. Particular preference is given here to permethrin, **cyphenothrin** in a concentration range of from 30 to 60% by weight.

(*Id.*, p. 4, ¶¶0015-0017, (emphasis added)). As to the types of formulations, the '542 publication continues: "The spot-on application is very particularly preferred." (*Id.*, p. 20, ¶0071).

Accordingly, a POSA would understand that on the whole, within the disclosure of the fipronil/cyphenothrin combination spot-on composition, there are a range of workable solutions. (EX1002, ¶61). A POSA would have experimented in a routine manner to find the workable ranges. (*In re Aller*, 220 F.2d 454 (C.C.P.A. 1955) (holding that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"; *see also*, EX1002, ¶61). Indeed, as Dr. Clark opines, the claims of the '542 publication recite the combination but do not limit the amount of α-cyanopyrethroid. Moreover, there is no disparagement

from the view of a POSA of any particular amount, or concentration of any α-cyanopyrethroid that can be present. (EX1002, ¶61). To a POSA, a preferred range is not a teaching away of any other disclosed ranges. *In re Fulton,* 391 F.3d 1195, 1201 (Fed. Cir. 2004) (holding that mere disclosure of alternative designs does not teach away); *see also*, *In re Mouttet,* 686 F.3d 1322, 1334 (Fed. Cir. 2012); *see also*, EX1002, ¶¶61, 66).

As September 2008 cyphenothrin was the obvious choice for an α-cyanopyrethroid because it was the only approved α-cyanopyrethroid in spot-on compositions for companion animals. (*Id*., ¶63). As discussed above, cyphenothrin possesses the desirable properties for inclusion in a spot-on composition for animals.

However, as Dr. Clark opines, due to cyphenothrin's associated toxicity at high amounts, the POSA would have been motivated to use as little as possible. (*Id*., ¶55). Accordingly, a POSA would have understood the '542 publication to teach a combination spot-on composition comprising fipronil and cyphenothrin, and that the cyphenothrin, as a known α-cyanopyrethroid, can be present in low concentrations, i.e., concentrations as low as 0.01% by weight. (*Id*., ¶62).

Though the '542 publication mentions cyphenothrin in the paragraph that discusses the Type I class of pyrethroids, a POSA would have known that cyphenothrin is structurally an α-cyanopyrethroid that exhibits Type II properties

as well as Type I properties. (*Id*., ¶64; *see also*, id., p. 22, n.3, for a summary of Types I and II). Given this backdrop, even though the '542 publication recites a "particular preference" of a range of 30% to 60% w/w for Type I pyrethroids, mentioning "permethrin, cyphenothrin" (EX1005, p. 4, ¶0017), a POSA would understand that much lower levels would work for cyphenothrin, too. (EX1002, ¶65). This is because cyphenothrin induces Type II symptoms as well as Type I symptoms. As such, a POSA would reasonably expect that cyphenothrin would work effectively at the lower levels as well, just as the other Type II α-cyanopyrethroids disclosed in the '542 publication.

During prosecution, the patent owner alleged that the '542 publication teaches away from using cyphenothrin at the lower concentrations associated with the Type II α-cyanopyrethroids. (EX1003, p. 085, patent owner's Response dated October 1, 2013, at p. 13, ll. 6-10. As Dr. Clark explains in his Declaration, the patent owner's allegations are incorrect. (EX1002, ¶66). First, considering the teachings of the '542 publication as a whole, a POSA would not be limited in his or her thinking with regard to only the amounts that are taught as preferred because levels that fall outside such preferred amounts would still be expected to work. (*Id*.). Again, this would be especially true because cyphenothrin exhibits Type II symptoms as well as Type I symptoms. (*Id*.). Second, as discussed below, other art, such as the '510 patent, teach that low amounts (e.g., 3 mg/kg) of an α-

cyanopyrethroid are effective against fleas and ticks on an animal for at least three weeks.

It is axiomatic that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including non-preferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804 (Fed. Cir. 1989). And the ’542 publication does not disparage non-preferred amounts or lead a POSA away from considering such amounts. (EX1002, ¶66). *In re Susi,* 440 F.2d 442 (CCPA 1971); *In re Mouttet,* 686 F.3d at 1334; *In re Fulton,* 391 F.3d at 1201.

b) The ’510 Patent

The ’510 patent (EX1006) issued on February 20, 1990, and is prior art under 102(b). The ’510 patent is not of record in the prosecution of the ’244 patent. As of the critical date, the ’510 patent evidences that cyphenothrin had already been formulated in insecticidal/parasiticidal compositions, including topical compositions for use against pests on animals. (EX1006, Abs.). With regard to the effective amounts, as Dr. Clark opines, the ’510 patent teaches topical compositions containing 0.75 to 7.5 % w/v of an alpha-cyanopyrethroid. (EX1002, ¶69). Further, in the ’510 patent, cyphenothrin is one of only 11 specific α-cyanopyrethroids listed. (*Id*., ¶70). Notwithstanding this low number of α-cyanopyrethroids from which to choose, as discussed above, as of the critical date,

cyphenothrin was the obvious choice. (*Id*., ¶63).

The ’510 patent teaches a topical pour-on formulation containing a synthetic pyrethroid, including specifically cyphenothrin, in amounts as low as 7.5 kg/m^3 (EX1006, col. 1, ll. 35-36), which corresponds to 0.75 % w/v. (EX1002, ¶69 and at p. 32, n.5). As disclosed in the ’510 patent, the pyrethroid is formulated for administration to an animal by “applying a liquid formulation of the insecticide to a localized region, preferably the dorsal spine, of the skin or coat of an animal to obtain an ectoparasiticidal effect over the whole body of the animal….” (EX1006, col. 1, ll. 12-15). The product is taught for use against ectoparasites, such as, ticks, on dogs. (*Id.*, col. 3, ll. 37-38).

2. Differences Between The Claims And The Prior Art

a) Claim 1 Would Have Been Obvious Over the ’542 Publication in Light of the ’510 Patent

Claim 1 merely requires localized administration on an animal of a spot-on composition comprising 8 to 11 % (w/w) fipronil, 3 to 16 % (w/w) cyphenothrin, and 60 to 80 % (w/w/) organic solvent. The following claim chart applies the prior art teachings of the ’542 publication and the ’510 patent:

Claim	Citation to Prior Art
1. A method of killing insect and pest pupae and adults on an animal,	“The compositions described herein are used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals.” **(The ’542 publication, p. 18, ¶ 0052)** “The method further provides a method of combating animal ectoparasites, e.g., ticks . . . .”

Claim	Citation to Prior Art
	(The '510 patent, at col. 3, ll. 37-38)
which method comprises administering a localized cutaneous application between the shoulders of the animal,	"All samples were applied as a single spot to the neck . . . ." **(The '542 publication, p. 25, ¶ 0086)** "Application may be by painting, spraying, pouring or by means of a dosing gun or syringe, conveniently to the back of the animal, e.g. in a line along the middle of the back of the animal between the base of the neck and base of the tail." **(The '510 patent, at col. 3, ll. 44-48)**
a spot-on composition comprising	"The spot-on application is very particularly preferred." **(The '542 publication, p. 20, ¶ 0071)**
8% to 11% (w/w) fipronil,	"An example of a very particularly preferred N-arylpyrazole is fipronil." **(*Id*., p. 14, ¶ 0030)** "Usually the compositions comprise the arylpyrazole in amounts from 1 to 27.5% by weight, preferably from 5 to 20% by weight, particularly preferred from 7.5 to 15% by weight. **(*Id*., p. 15, ¶ 0038)**
3% to 16% (w/w) cyphenothrin,	The α-cyanopyrethroid is present "from 0.01 to 5% by weight." **(The '542 publication, p. 4, para. 0016)** "[F]ormulation comprising a pyrethroid insecticide at a concentration of 7.5 to 75 kg/m^3 . . . ." **(The '510 patent, at 1:35-36)**. As discussed *supra*, this corresponds to ***0.75% to 7.5% w/v***. Cyphenothrin is one of only 11 α-cyanopyrethroids specifically disclosed in the '510 patent **(*Id*., col. 2, ll. 15-39)**.
and 60% to 80% (w/w) organic solvent.	"The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." **(The '542 publication, p. 16, ¶ 0040)**

As discussed above and in reference to the claim chart, as of the critical date,

the prior art had already disclosed the combination of an α-cyanopyrethroid, such as cyphenothrin, at a low concentration in topical formulations (the ’542 publication and the ’510 patent) in combination with fipronil (the ’542 publication) for use on animals to combat ectoparasites (both references). Because the prior art had already taught the claimed combination and its uses in a spot-on composition, the only difference between the method claims of the ’244 patent and the prior art discussed above is the specific amount of cyphenothrin—3% to 16% (w/w) or 4% to 6% (w/w)—in the spot-on composition.

With respect to the concentrations disclosed in the prior art, the ’542 claims the combination of an N-arylpyrazole and an α-cyanopyrethroid without any specific limitations on the amounts present. The ’542 publication also discloses specific amounts and a POSA would have been taught that α-cyanopyrethroids can be used “in a concentration range from of from 0.01 to 5% by weight.” (EX1005, p. 4, ¶0016; *see also*, EX1002, ¶78). Additionally, the examples in the ’542 publication describe compositions with the α-cyanopyrethroid, flumethrin, at a concentration of 0.24% (w/v). (EX1002, ¶78).

Moreover, a POSA would have been aware that the ’510 patent had already shown that low concentrations of α-cyanopyrethroids (3 mg/kg) work (94.5% efficacy at 21 days) as a topical parasiticide. (EX1002, ¶82). The ’510 patent teaches topical pour-on formulations containing 0.75% to 7.5% w/v cyphenothrin,

and even lower concentrations of 1.0% to 3.0% w/v and specifically 1.5% w/v. (*Id*.). To a POSA, any amounts within these ranges have an expectation that they would work, especially in light of the Examples in the '510 patent, which show that a low dose (3 mg/kg) of the α-cyanopyrethroid, alpha-cypermethrin, was effective against ticks for over 21 days. (EX1006, col. 6, l. 39 through col. 7, l. 13; *see also*, EX1002, ¶83). Also, there are only 11 α-cyanopyrethroids specifically disclosed in the '510 patent and one of them is cyphenothrin (EX1002, ¶84), which as discussed above would have been the obvious choice. (*See also*, *id*., ¶63).

There is another reason a POSA would have reasonably expected cyphenothrin to be effective at such low concentrations. That is, because of the additive effect of combining fipronil with cyphenothrin, a POSA would have reasonably expected to be able to use lower doses and concentrations of cyphenothrin in an effective combination spot-on composition. (*Id*., ¶¶88-89). Fipronil was well known in the art to be one of the most successful topical anti-flea and tick products, and was known to be >95% effective for at least five weeks against fleas. (*Id*., ¶89). As such, a POSA would have known that the action of fipronil would contribute to the killing power of the combination product, thereby allowing for the use of a lower amount of one or both of the active agents without the loss of efficacy.

b) A POSA Would Have Been Motivated to Combine the '542 Publication with the '510 Patent

As of September 2008, cyphenothrin was a known α-cyanopyrethroid that had been used in a spot-on composition for the very same purpose in a product known as "Sergeant's® Gold Squeeze-on For Dogs," which was a 40% cyphenothrin, 50 mg/kg spot-on composition. (*Id*., ¶85). That product, while purportedly possessing the desired efficacy, nevertheless suffered from the known toxicity drawbacks associated with high dosages of cyphenothrin, such as paresthesia. (*Id*.). As a result, a POSA would have naturally been motivated to reduce the level of cyphenothrin without sacrificing efficacy and duration. (*Id*.).

A POSA would have been aware of the teachings of the '510 patent with regard to effectiveness of very low dosages of a handful of α-cyanopyrethroids, including cyphenothrin, in a pour-on formulation for the topical treatment of insects and ticks on animals. Accordingly, the POSA would have been motivated to use the low concentration and dosages disclosed in the '510 patent (3 mg/kg) with the spot-on combination composition of the '542 publication. (*Id*., ¶86). Additionally, a POSA would have been motivated to combine low concentration cyphenothrin with fipronil because of their complementary nature (i.e., quick-kill properties of cyphenothrin and the properties of fipronil, which include relatively longer-lasting efficacy yet slower-acting activity). (*Id*., ¶¶58 and 87).

c) A POSA Would Have Had a Reasonable Expectation

of Success

Finally, a POSA would have had a reasonable expectation that the low dose combination spot-on composition would have the desired efficacy because the '510 patent discloses that low dose (3 mg/kg), topical α-cyanopyrethroids can be ≥ 94.5% effective against ticks on cattle for over 21 days. (EX1006, col. 6, data in Example 15, Table III; assay protocol described in Example 13, beginning at col. 5, l. 46; "overall reduction in tick survival over the 21 day period after application" *id*., col. 6, ll. 18-19; *see also* EX1002, ¶88). In addition, the '542 publication discloses low dose (exemplified by a dosage of 0.24 mg/kg) α-cyanopyrethroids in combination with fipronil in a spot-on formulation. (EX1002, ¶88).

Moreover, combining fipronil with cyphenothrin would be expected to provide high efficacy against fleas and ticks. Fipronil was well known in the art to be one of the most successful topical anti- flea and tick products, and was known to be >95% effective for at least five weeks against fleas. (EX1010, p. 397, last sentence; *see also* EX1002, ¶89). Therefore, a POSA would have known that the action of fipronil would significantly contribute to the killing power of the combination product. That is, at the very least, an additive effect of the combined actives would have been reasonably expected. As such, combining fipronil with cyphenothrin would have been reasonably expected to facilitate using low doses and concentrations of cyphenothrin in an effective combination spot-on

composition, thereby providing a beneficial reduction in the amount of cyphenothrin used, but without any reduction in long-lasting efficacy.

In light of these teachings and the reasonable expectation of success, a POSA would only have to adjust the amount of cyphenothrin to within the disclosed ranges of the ’510 patent and the ’542 publication, which is an exercise that would be considered routine optimization and well within the ordinary skill of a POSA. (*In re Aller*, F.2d 456-57). For a POSA, there is nothing inventive in such a routine exercise. (*In re Peterson,* 315 F.3d 1325 (Fed. Cir. 2003)).

Alternatively, it would have been obvious to try a method for combating pests using a spot-on composition having the claimed amounts of cyphenothrin and fipronil. During prosecution, the patent holder admitted that it was known that topical administration of high doses of cyphenothrin caused a skin condition known as paresthesia. (EX1003, pp. 230-231, Nouvel Declaration I, sentence bridging pp. 3-4). There were a finite number of solutions to this problem—the most obvious of which would have been to choose to use less cyphenothrin. Combining cyphenothrin with a second active, namely, fipronil, as the ’542 publication suggests would facilitate the use of lower concentrations of cyphenothrin without sacrificing efficacy or duration. As discussed above, there would have been a reasonable expectation of success in doing so based on two straightforward teachings in the prior art: the combination of cyphenothrin and

fipronil in a spot-on composition ('542 publication); and low concentrations of cyphenothrin in pour-on formulations where the exemplified α-cyanopyrethroids, alphacypermethrin and cypermethrin, were ≥ 94.5% efficacious against ticks over the 21 days of testing ('510 patent).

d) Claim 2 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 2 depends from claim 1 and merely adds that the cyphenothrin is present in the composition in a concentration of 4 to 6 % (w/w). As such, the claimed amount of cyphenothrin falls entirely within the amounts of pyrethroid disclosed in the '510 patent's range of 0.75 to 7.5% (w/v). (EX1002, ¶93). Not only is the claimed range subsumed by the '510 patent, there is also considerable overlap of the claimed range and the much narrower amounts of alpha-cyanopyrethroids in the '542 publication's range of "from 0.01 to 5% by weight." (EX1005, p. 2, ¶0018; EX1002, ¶¶92-94). There is nothing inventive about selecting a workable range within a broader or overlapping range described in the prior art. (*In re Peterson* 315 F.3d 1325). Accordingly, claim 2 would have been obvious over the '542 publication in light of the '510 patent.

e) Claims 3 and 4 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 4 depends from claim 3, which itself depends from claim 1. Claim 3 merely recites that the animal is a mammal, and claim 4 merely adds that the mammal is a dog or cat. The '542 publication teaches that the spot-on

compositions are "used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals." (EX1005, p. 18, ¶0052). The '510 patent is directed to treating pests on an animal and each of these elements are explicitly taught by the '510 patent: "[A]n animal, e.g., selected from cattle, sheep, goats, pigs, dogs, horses, deer and cats." (EX1006, col. 3, ll. 41-43). Accordingly, claims 3 and 4 would have been obvious over the '542 publication in light of the '510 patent.

f) Claims 5 and 6 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 6 depends from claim 5, which itself depends from claim 1. Claim 5 merely recites that the composition additionally comprises an "insect growth regulator" ("IGR"), and claim 6 merely adds that the "insect growth regulator" is present in a concentration of between 2 to 15 % (w/w). Although the claims do not identify what constitutes an "insect growth regulator", the '244 patent teaches that a preferred insect growth regulator is S-methoprene. (EX1001, col. 15, ll. 17-18).

One of the most well-known IGRs as of the critical date is S-methoprene, which is a component of Frontline Plus®, which has been on the market since before the critical date. (EX1002, ¶98). In fact, the '542 publication explicitly teaches adding the methoprene (i.e., S-methoprene) to its N-arylpyrazole and pyrethroid combination spot-on compositions: "In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or

more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … methoprene." (EX1005, pp. 17-18, ¶0048). Because S-methoprene is one of the most widely used IGRs, it would have been an obvious IGR for a POSA to choose for a spot-on formulation to combat ectoparasites on dogs and cats. (EX1002, ¶98).

Moreover, a POSA would have known of the appropriate amount of S-methoprene from the art in general, including that for the registered product Frontline® Plus, which contains 8.8% S-methoprene, and from the '542 publication itself. (*Id*., ¶99). The amount disclosed in the '542 publication of "from 0.1 to 7.5% by weight" (EX1005, pp. 17-18, ¶0048) overlaps the claimed amount. Accordingly, claims 5 and 6 would have been obvious over the '542 publication in light of the '510 patent. (*In re Aller*, 220 F.2d at 456-57).

g) Claim 7 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 7 depends from claim 1. Claim 7 merely adds that the composition of claim 1 can additionally comprises an antioxidant at 4 to 6 % (w/w). As of September 2008, a POSA was would have been well aware that antioxidants are common excipients in spot-on compositions. (EX1002, ¶101). Indeed, the '542 publication and the '510 patent teaches that additives in its compositions may include antioxidants. (EX1005, p. 17, ¶0044; EX1006, col. 3, l. 9).

To a POSA, reaching the recited amount of antioxidant in claim 7 of the

’244 patent would have been a mere routine exercise in optimizing the amount of a well-known excipient in these types of formulations. (EX1002, ¶101). Since adding an antioxidant to topical insecticidal compositions was standard practice at the time, claim 7 would have been obvious as of September 2008 for the same reasons as claim 1. (*In re Aller*, 220 F.2d at 456-57). Accordingly, claim 7 would have been obvious over the ’542 publication in light of the ’510 patent.

h) Claims 10-15 Would Have Been Obvious Over the ’542 Publication in Light of the ’510 Patent

Independent claim 10 recites a method of killing insect and pest pupae and adults comprises administering a spot-on composition comprising: 8 to 11 % (w/w) fipronil; 4 to 6 % (w/w) cyphenothrin; 70 to 80 % (w/w) organic solvent; and 4 to 6 % (w/w) antioxidant. Thus, claim 10 is the same as claim 1, except that it incorporates the elements of claim 2 (4-6 % (w/w) cyphenothrin); the elements of claim 7 (4 to 6 % (w/w) antioxidant); and further requires that the organic solvent is present in an amount of 70 to 80 % (w/w).

It would have been an obvious choice for a POSA to select the components recited in claim 10 because all claim 10 requires is the use of components in ranges that are encompassed or overlapped by the ranges disclosed in the ’542 publication and the ’510 patent. To a POSA, selecting every element of claim 10 only requires using known components for the very same purpose and in the very same amounts for which they are known in the art. As such, claim 10 (as well as any of its

dependent claim) would have been obvious for the very same reasons as discussed above for claims 1, 2 and 7. Moreover, in reference to Claim 12, which recites "the antioxidant is tocopherol nicotinate" i.e., Vitamin E, as Dr. Clark opines, Vitamin E was known by a POSA to be a customary antioxidant for topical compositions as of the critical date. (EX1002, ¶105). Claim charts presented below provide a comparison of claims 10-15 with the prior art.

Claim	Citation to Prior Art
10. A method of killing insect and pest pupae and adults on an animal,	"The compositions described herein are used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals." **(The '542 publication, p. 18, ¶0052)** "The method further provides a method of combating animal ectoparasites, e.g., ticks . . . ." **(The '510 patent, col. 3, ll. 37-38)**
which method comprises administering a localized cutaneous application between the shoulders of the animal,	"All samples were applied as a single spot to the neck . . . ." **(The '542 publication, p. 25, ¶0086)** "Application may be by painting, spraying, pouring or by means of a dosing gun or syringe, conveniently to the back of the animal, e.g. in a line along the middle of the back of the animal between the base of the neck and base of the tail." **(The '510 patent, col. 3, ll. 44-48)**
a spot-on composition comprising:	"The spot-on application is very particularly preferred." **(The '542 publication, p. 20, ¶0071)**
a. 8% to 11% (w/w) fipronil;	"An example of a very particularly preferred N-arylpyrazole is fipronil." **(*Id*., p. 14, ¶0030)** "Usually the compositions comprise the arylpyrazole in amounts from 1 to 27.5% by weight, preferably from 5 to 20% by weight, particularly preferred from 7.5 to 15% by weight.

Claim	Citation to Prior Art
	(*Id*., p. 15, ¶0038)
b. 4% to 6% (w/w) cyphenothrin;	The α-cyanopyrethroid is present "from 0.01 to 5% by weight." **(The '542 publication, p. 4, ¶0016)** "[F]ormulation comprising a pyrethroid insecticide at a concentration of 7.5 to 75 kg/m^3 . . . ." **(The '510 patent, col. 1, ll. 35-36)** As discussed *supra*, this corresponds to ***0.75% to 7.5% w/v***. Cyphenothrin is one of only 11 α-cyanopyrethroids specifically disclosed in the '510 patent **(*Id*., col. 2, ll. 15-39)**
c. 70% to 80% (w/w) organic solvent; and	"The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." **(The '542 publication, p. 16, ¶0040)**
d. 4% to 6% (w/w) antioxidant.	As discussed *supra*, the amount of antioxidant would have been obvious in light of the teachings of an antioxidant in the **'510 patent at col. 3, ll. 8-9**. *See also*, the **'542 publication, p. 17, ¶0044**.
11. The method of claim 10,	
wherein the organic solvent is diethylene glycol monoethyl ether.	"preferred examples: are diethylene glycol monoethyl ether." **(The '542 publication, p. 16, ¶0041)**
12. The method of claim 10,	
wherein the antioxidant is tocopherol nicotinate.	As discussed *supra*, selecting tocopherol nicotinate would have been an obvious choice because it is a customary antioxidant.
13. The method of claim 12,	
wherein the organic solvent is diethylene glycol monoethyl ether.	"preferred examples: are diethylene glycol monoethyl ether." **(The '542 publication, p. 16, ¶0041)**
14. The method of claim 12,	
wherein the composition further comprises 2% to	"In addition to the arylpyrazoles and pyrethroids, the compositions according to the

Claim	Citation to Prior Art
15% (w/w) insect growth regulator.	invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … methoprene." **(*Id*., ¶ 0048, bridging pp. 17-18)** As discussed *supra*, as of the critical date, methoprene is a well-known insect growth regulator. "[A]mount may be varied within wide limits in the range of from 0.1 to 7.5% by weight, but preferably from 0.25 to 5.0% by weight, particularly preferably from 0.25 to 2.5% by weight." **(*Id*., p. 18, ll. 5-7)**
15. The method of claim 14,	
wherein the insect growth regulator comprises pyriproxyfen or S-methoprene.	As discussed *supra*, methoprene comprises R and S forms. *See also*, **EX1002, ¶98**

i) Claims 16-18 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Independent claim 16 recites a method of killing insect and pest pupae and adults comprising administering a spot-on composition that includes: 8 to 11 % (w/w) fipronil; 4 to 6 % (w/w) cyphenothrin; 8 to 12 % (w/w) S-methoprene; 70 to 80 % (w/w) organic solvent; and 4 to 6 % (w/w) antioxidant. Thus, claim 16 is the same as claim 10, except that it incorporates S-methoprene in the recited amount. As such, claim 16 (as well as any dependent claim) would have been obvious for the very same reasons as discussed above for claims 10 and 15.

With regard to dependent claims 17 and 18, all these claims further require

are that the animal is a mammal in the case of claim 17, and that the mammal is a dog or cat in the case of claim 18. Each of these elements is found in the '542 publication and/or the '510 patent as shown in the claim chart below. (*See also*, EX1002, ¶111). Claim charts presented below provide a comparison of claims 16-18 with the prior art:

Claim	Citation to Prior Art
16. A method of killing insect and pest pupae and adults on an animal,	"The compositions described herein are used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals." **(The '542 publication, p. 18, ¶0052)** "The method further provides a method of combating animal ectoparasites, e.g., ticks . . . ." **(The '510 patent, col. 3, ll. 37-38)**
which method comprises administering a localized cutaneous application between the shoulders of the animal,	"All samples were applied as a single spot to the neck . . . ." **(The '542 publication, p. 25, ¶0086)** "Application may be by painting, spraying, pouring or by means of a dosing gun or syringe, conveniently to the back of the animal, e.g. in a line along the middle of the back of the animal between the base of the neck and base of the tail." **(The '510 patent, col. 3, ll. 44-48)**
a spot-on composition comprising:	"The spot-on application is very particularly preferred." **(The '542 publication, p. 20, ¶0071)**
a. 8% to 11% (w/w) fipronil;	"An example of a very particularly preferred N-arylpyrazole is fipronil." **(*Id*., p. 14, ¶0030)** "Usually the compositions comprise the arylpyrazole in amounts from 1 to 27.5% by weight, preferably from 5 to 20% by weight, particularly preferred from 7.5 to 15% by weight. **(*Id*., p. 15, ¶0038)**
b. 4% to 6% (w/w) cyphenothrin;	The α-cyanopyrethroid is present "from 0.01 to 5% by weight." **(*Id*., p. 4, ¶0016)** "[F]ormulation comprising a pyrethroid insecticide at a concentration of 7.5 to 75 kg/m^3 . . . ."

Claim	Citation to Prior Art
	(The '510 patent, col. 1, ll. 35-36) As discussed *supra*, this corresponds to ***0.75% to 7.5% w/v***. Cyphenothrin is one of only 13 α-cyanopyrethroids specifically disclosed in the '510 patent **(*Id*., col. 2, ll. 15-39)**
c. 8% to 12% (w/w) S-methoprene;	"In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … methoprene." **(The '542 publication, ¶0048, bridging pp. 17-18)** As discussed *supra*, selecting methoprene and the appropriate amount to use would have been an obvious choice to a POSA.
d. 70% to 80% (w/w) organic solvent; and	"The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." **(*Id*., p. 16, ¶0040)**
e. 4% to 6% (w/w) antioxidant.	As discussed *supra*, the amount of antioxidant would have been obvious in light of the teachings of an antioxidant in the **'510 patent at col. 3, ll. 8-9**.
17. The method of claim 16 wherein the animal is a mammal.	"[t]he compositions described are used in particular against ectoparasites on pets, in particular dogs and cats … ." **(The '542 publication, p. 18, paragraph 0052)** "[A]n animal, e.g., selected from cattle, sheep, goats, pigs, dogs, horses, deer and cats." **(The '510 patent, column 3, ll. 41-43)**
18. The method of claim 17 wherein the mammal comprises a dog or a cat.	See supra, claim 17.

j) Claim 19 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 19 is an independent claim. It recites that the method of killing insect

and pest pupae and adults comprises administering a spot-on composition comprising: 8 to 11 % (w/w) fipronil; 4 to 6 % (w/w) cyphenothrin; 3 to 5 % (w/w) pyripoxyfen; 70 to 80 % (w/w) organic solvent; and 4 to 6 % (w/w) antioxidant. Thus, claim 19 is the same as claim 10, except that it incorporates pyripoxifen in the recited amount. A POSA would have known that it was standard practice to include an additional active, particularly pyriproxyfen. (EX1002, ¶113). Indeed, a POSA is led to pyriproxyfen as one of only three species of juvenile hormone analogues in the '542 publication: "In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: . . . juvenile hormone analogues (for example methoprene, hydroprene, pyriproxyfen) . . . ." (EX1005, ¶0048 bridging pp. 17-18). Moreover, claimed amount of pyriproxyfen overlaps the amount disclosed in the '542 publication of "from 0.1 to 7.5% by weight." (*Id*., p. 18, ll. 5-7). As such, claim 19 would have been obvious for the very same reasons that claim 10 would have been obvious. The claim chart presented below provides a comparison of claim 19 with the prior art:

Claim	Citation to Prior Art
19. A method of killing insect and pest pupae and adults on an animal,	"The compositions described herein are used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals." **(The '542 publication, p. 18, ¶0052)**

Claim	Citation to Prior Art
	"The method further provides a method of combating animal ectoparasites, e.g., ticks . . . ." **(The '510 patent, col. 3, ll. 37-38)**
which method comprises administering a localized cutaneous application between the shoulders of the animal,	"All samples were applied as a single spot to the neck . . . ." **(The '542 publication, p. 25, ¶0086)** "Application may be by painting, spraying, pouring or by means of a dosing gun or syringe, conveniently to the back of the animal, e.g. in a line along the middle of the back of the animal between the base of the neck and base of the tail." **(The '510 patent, col. 3, ll. 44-48)**
a spot-on composition comprising:	"The spot-on application is very particularly preferred." **(The '542 publication, p. 20, ¶0071)**
a. 8% to 11% (w/w) fipronil;	"An example of a very particularly preferred N-arylpyrazole is fipronil." **(*Id.*, p. 14, ¶0030)** "Usually the compositions comprise the arylpyrazole in amounts from 1 to 27.5% by weight, preferably from 5 to 20% by weight, particularly preferred from 7.5 to 15% by weight." **(*Id.*, p. 15, ¶0038)**
b. 4% to 6% (w/w) cyphenothrin;	The α-cyanopyrethroid is present "from 0.01 to 5% by weight." **(*Id.*, p. 4, para. 0016)** "[F]ormulation comprising a pyrethroid insecticide at a concentration of 7.5 to 75 kg/m^3 . . . ." **(The '510 patent, at 1:35-36)**. As discussed *supra*, this corresponds to ***0.75% to 7.5% w/v***. Cyphenothrin is one of only 13 α-cyanopyrethroids specifically disclosed in the '510 patent **(*Id.*, col. 2, ll. 15-39)**.
c. 3% to 5% (w/w) pyriproxyfen;	"In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … pyriproxyfen." **(The '542 publication, ¶0048, bridging pp. 17-18)** "[A]mount may be varied within wide limits in

Claim	Citation to Prior Art
	the range of from 0.1 to 7.5% by weight, but preferably from 0.25 to 5.0% by weight . . . ." **(*Id*., p. 18, ll. 5-7)** As discussed *supra*, selecting pyriproxyfen and the appropriate amount to use would have been an obvious choice to a POSA.
d. 70% to 80% (w/w) organic solvent; and	"The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." **(*Id.*, p. 16, ¶0041)**
e. 4% to 6% (w/w) antioxidant.	As discussed *supra*, the amount of antioxidant would have been obvious in light of the teachings of an antioxidant in the **'510 patent at column 3, ll. 8-9**. *See also*, the **'542 publication, p. 17, ¶0044**.

k) Claims 20-22 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent

Claim 20 is an independent claim. It recites that the method of killing insect and pest pupae and adults comprises administering a spot-on composition comprising: 8 to 11 % (w/w) fipronil; 4 to 6 % (w/w) cyphenothrin; and 70 to 80 % (w/w) diethylene glycol monoethyl ether. Thus, claim 20 is the same as claim 1, except that it specifies that the organic solvent is diethylene glycol monoethyl ether and it is present at a narrower range relative to claim 1. The '542 publication teaches that: "The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." (EX1005, p. 16, ¶0041); and that: "preferred examples: are diethylene glycol monoethyl ether." (*Id*.). Thus, claim 20 would

have been obvious for the very same reasons that claim 1 would have been obvious because the ’542 publication also teaches the claimed solvent and amounts.

With regard to the claims that depend from claim 20, claim 21 merely adds that the composition further comprises 3 to 5 % pyripoxyfen, which is analogous to claim 19. Claim 22 merely adds that the composition of claim 20 further comprises 8 to 12 % (w/w) S-methoprene, which is analogous to claim 16. As such, claims 21 and 22 would have been obvious for the very same reasons as claims 16 and 19. The claim chart presented below provide a comparison of claims 20-22 with the prior art:

Claim	Citation to Prior Art
20. A method of killing insect and pest pupae and adults on an animal,	“The compositions described herein are used in particular against ectoparasites on pets, in particular dogs and cats, and useful animals.” **(The ’542 publication, p. 18, ¶0052)** “The method further provides a method of combating animal ectoparasites, e.g., ticks . . . .” **(The ’510 patent, col. 3, ll. 37-38)**
which method comprises administering a localized cutaneous application between the shoulders of the animal,	“All samples were applied as a single spot to the neck . . . .” **(The ’542 publication, p. 25, ¶0086)** “Application may be by painting, spraying, pouring or by means of a dosing gun or syringe, conveniently to the back of the animal, e.g. in a line along the middle of the back of the animal between the base of the neck and base of the tail.” **(The ’510 patent, col. 3, ll. 44-48)**
a spot-on composition comprising:	“The spot-on application is very particularly preferred.” **(The ’542 publication, p. 20, ¶0071)**
a. 8% to 11% (w/w)	“An example of a very particularly preferred N-

fipronil;	arylpyrazole is fipronil." **(*Id*., p. 14, ¶0030)** "Usually the compositions comprise the arylpyrazole in amounts from 1 to 27.5% by weight, preferably from 5 to 20% by weight, particularly preferred from 7.5 to 15% by weight. **(*Id*., p. 15, ¶0038)**
b. 4% to 6% (w/w) cyphenothrin; and	The α-cyanopyrethroid is present "from 0.01 to 5% by weight." **(The '542 publication, p. 4, ¶0016)** "[F]ormulation comprising a pyrethroid insecticide at a concentration of 7.5 to 75 kg/m^3 . . . ." **(The '510 patent, at col. 1, ll. 35-36)**. As discussed *supra*, this corresponds to ***0.75% to 7.5% w/v***. Cyphenothrin is one of only 13 α-cyanopyrethroids specifically disclosed in the '510 patent **(*Id*., col. 2, ll. 15-39)**.
c. 70% to 80% (w/w) diethylene glycol monoethyl ether.	"The amount of aliphatic, cyclic and/or acyclic ether in the compositions according to the invention can be varied within wide limits of from 20 to 77.5% by weight . . . ." **(The '542 publication, p. 16, ¶0041)** "preferred examples: are diethylene glycol monoethyl ether." **(*Id*.)**
21. The method of claim 20,	
wherein the composition further comprises 3% to 5% (w/w) pyriproxyfen.	"In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … pyriproxyfen." **(*Id*., ¶0048 bridging pp. 17-18)** As discussed *supra*, pyriproxyfen is one of only three such compounds listed in the '542 publication. "[A]mount may be varied within wide limits in the range of from 0.1 to 7.5% by weight, but preferably from 0.25 to 5.0% by weight,

	particularly preferably from 0.25 to 2.5% by weight." **(*Id.*, p. 18, ll. 5-7)**
22. The method of claim 20,	
wherein the composition further comprises 8% to 12% (w/w) S-methoprene.	"In addition to the arylpyrazoles and pyrethroids, the compositions according to the invention may also comprise one or more additional active compounds. Preferred examples of such active compounds for combinations which may be mentioned are: … methoprene." **(*Id.*, ¶0048, bridging pp. 17-18)** As discussed *supra*, methoprene is one of only three such compounds listed in the '542 publication) and it is a well-known ectoparasiticide. As such, selecting the claimed amount of S-methoprene would have been an obvious choice.

D. Ground 2: Claims 8 and 9 Would Have Been Obvious Over the '542 Publication in Light of the '510 Patent and the EPA Product Performance and Efficacy Report

1. The Subject Matter of Claims 8 and 9

Claim 8 depends from claim 1 and further requires that the composition provides at least 90% efficacy against insect and pest pupae for a period of at least 30 days following administration of the composition to the animal. As such, claim 8 merely recites an expected properties of the claimed composition. *Santarus, Inc. v. Par Pharma., Inc.*, 694 F.3d 1344 (Fed. Cir. 2012). Claim 9 further requires administering the composition in a volume sufficient to deliver a dosage of cyphenothrin from about 0.1 mg/kg to about 40 mg/kg. All of these elements are rendered obvious by the combination of the '542 publication, the '510 patent and the EPA Product Performance and Efficacy Report (hereinafter, "the EPA

Report").

2. Scope and Content of the Prior Art

The '542 publication and the '510 patent are discussed above. For brevity, that discussion is not repeated here. The EPA Report is discussed below.

a) The EPA Report

The EPA Report was publically available as of the product registration date of November 2006. (EX1002, p. 34, n.6). As such it is available as a 102(b) reference. The EPA Report detailing patent owner's own studies is not of record in the '244 patent, but was submitted in front of the Environmental Protection Agency in 2006 during the registration process for a 40% cyphenothrin-containing spot-on composition. (*Id*., ¶122).

The study reports on a spot-on formulation containing cyphenothrin: "For the brown dog tick, the data demonstrate that cyphenothrin provides a greater than 90% reducting [sic], relative to the control group mean, for up to **30 days** at the **25 mg/kg rate** . . . ." (EX1007, p. 3/31, under MRID 46166110; *see also*, EX1002, ¶73). With regard to fleas, the study also concluded that: "The study compared the number of parasites found on test animals following a dose of 0, 25, or 100 mg/kg. Against fleas, the data demonstrate that cyphenothrin provides a greater than 90% reducting, relative to the control group mean, for up to **23 days** at the **25 mg/kg rate** . . . ." (*Id*., (emphasis added)).

The data in the EPA Report show that the concentration is not critical for

duration of efficacy, *but rather it is the dosage that matters*. (EX1002, ¶74). As Dr. Clark opines, the dosages applied in the EPA Report vary from 0 to 100 mg/kg though concentration of cyphenothrin in the formulation remains constant. (*Id*.). Again, as Dr. Clark opines, the EPA Report plainly shows that at the very same *concentrations*, a *dosage* of 100 mg/kg has efficacy of over 90% for fleas for 35 days whereas the same *concentration* of cyphenothrin at a *dosage* of 25 mg/kg has efficacy over 90% for fleas for 23 days. (*Id*.).

Given the importance of dosage, a POSA would also understand from this teaching that a relatively small dosage (25 mg/kg) that corresponds to only 25% of that of the larger 100 mg/kg dose still provides over 90% efficacy for 65% of the duration. (*Id*.). Put another way, reducing the dosage does not result in an equal decrease in activity. The end result is that a POSA would have concluded that for cyphenothrin there is no *linear* correlation between dosage and the duration of efficacy against fleas and ticks on dogs. (*Id*.).

Importantly, in the EPA Report, cyphenothrin is acting alone. (*Id*., ¶75). That is, there is no other parasiticide present. As Dr. Clark opines, cyphenothrin, even though it is acting alone, at a *dosage* of 25 mg/kg cyphenothrin has greater than 90% efficacy at 23 days against fleas and greater than 90% efficacy at 30 days against the brown dog tick. (*Id*.). Adding a second parasiticide (i.e., fipronil) would have led to at least an additive effect of two agents because of their

complementary mechanisms of action, as discussed above. To a POSA, it would be entirely expected that in the presence of fipronil, even lower dosages of cyphenothrin would provide long-lasting (about 4 weeks) efficacy at the same level as that of a formulation containing cyphenothrin alone at a higher concentration. (EX1002, ¶76). That is to say, a POSA would expect that the activity of fipronil would substantially contribute to, and even improve, upon the overall killing power of the cyphenothrin-only composition in the EPA Report. (*Id*.).

3. Differences Between The Claims And The Prior Art

As discussed above, the state of the art as of the critical date would have rendered base claim 1 obvious. Claim 8 depends from claim 1 and merely adds the element of providing "at least 90% efficacy against insect and pest pupae for a period of at least 30 days following administration of the composition to the animal." To the extent that claim 8 is directed to efficacy against *pupae*, the '542 publication discloses the inclusion of S-methoprene. As Dr. Clark opines, S-methoprene, as an IGR, would be efficacious against insect and pest pupae because it prevents pupae from forming. (*Id*., p. 48, n.9). Moreover, as Dr. Clark opines, a POSA would have known that S-methoprene would have been at least 90% efficacious for 30 days. (EX1002, ¶98 and p. 48, n.9; *see also*, EX1010, p. 401, Table 1, showing larval hatch data and 98.9% efficacy of S-methoprene at 29 days). Another way a POSA would have known to address pupae is by killing

them as they emerge from the pupal stage by the quick-kill and long-acting activity of the cyphenothrin/fipronil combination.

A POSA would have been motivated to add S-methoprene to the combination because it is commonly included in spot-on compositions and has well-known and desirable properties, such as efficacy against the formation of pupae. (EX1002, ¶98, and p. 48, n.9). There would have been a reasonable expectation of success that such a composition would have the desired efficacy and duration against the formation of pupae or emerging fleas because the known activity of each of the active agents provides these properties.

Claim 9 depends from claim 1 and merely adds an additional element with regard to the dosage of cyphenothrin. Claim 9 recites, "a dosage of cyphenothrin ranging from about 0.1 mg/kg to about 40 mg/kg." This element is clearly disclosed in the patent owner's own studies which had published in 2006, just after its product received EPA registration.

To a POSA, the EPA Report shows that at *dosages* well within the range recited in claim 9, cyphenothrin works up to 30 days at a level of at least 90% efficacy. (EX1002, ¶123). The dosage takes into account both the weight of the animal and the concentration to provide the amount of cyphenothrin per animal weight (i.e., mg/kg) that has been applied to the animal. (EX1002, ¶125, and n.12, explaining that dosages are used in studies so that amount in mg active/kg body

weight can be compared and not simply concentration). To a POSA, this plainly means that the dosage of cyphenothrin covered by claim 9 is the same dosage disclosed in the EPA Report. (EX1002, ¶123). Accordingly, a POSA having read and considered the teachings of the EPA Report is made aware that a *dosage* of 25 mg/kg of cyphenothrin is over 90% efficacious against ticks for as long as 30 days. Said another way, the EPA Report teaches a *dosage* that falls squarely in the middle of the claimed range of "about 0.1 to about 40 mg/kg."

The patent owner may argue that the EPA Report is not relevant because it deals with a high concentration (40%) cyphenothrin composition whereas the claims cover low concentration of cyphenothrin. As explained by Dr. Clark, despite the fact that the concentrations are different, a POSA would consider the teachings of the EPA Report in terms of dosages because dosage describes the amount of cyphenothrin per animal weight that was applied, i.e., that 25 mg/kg dosage is effective for 30 days against ticks. (EX1002, ¶125). Even the patent owner admitted during prosecution that two different concentrations applied at the same dosage would be expected to yield "the same duration of efficacy." (EX1003, p. 160, patent owner's Response dated May 15, 2013, at p.12, second full paragraph, stating "according to known principles, as illustrated by the data submitted herewith, the two treatments would be expected to provide the same duration of efficacy, despite the fact that the two compositions contained different

concentrations of cyphenothrin."); *see also*, EX1002, ¶125).

Given the similarities between the limitations of claims 8 and 9, the same motivation to combine and reasonable expectation of success rationale as discussed above with regard to claim 8, applies equally to claim 9.

Alternatively, it would have been obvious to try a method for combating insect and pest pupae using a spot-on composition at the claimed dosage range with an expectation that it would work at least as long as the claimed time period. During prosecution, the patent holder admitted that it was known that topical administration of high doses of cyphenothrin caused a skin condition known as paresthesia. (EX1003, pp. 230-231, Nouvel Declaration I, sentence bridging pp. 3-4). There were a finite number of solutions to this problem, the best choice being to use a low amount of cyphenothrin, which was already approved for the exact same use in a spot-on composition, in combination with a second active, namely, fipronil, as the '542 publication suggests. The reasonable expectation of success in such a combination has been described above and is confirmed by Dr. Clark. (EX1002, ¶127).

The claim chart presented below provide a comparison of claims 8 and 9 with the prior art:

Claim	Citation to Prior Art
8. The method of claim 1,	See *supra*, for all the elements of claim 1
wherein the composition provides at least 90%	These elements merely recite a property of the obvious composition. The properties would have

Claim	Citation to Prior Art
efficacy against insect and pest pupae for a period of at least 30 days following administration of the composition to the animal.	also been obvious. See *supra*, discussing the efficacy and duration of S-methoprene, which acts to prevent maturation into pupae. Further, see *supra*, discussing the efficacy and duration data disclosed in the **EPA Report** that would render the claimed properties obvious to a POSA.
9. The method of claim 1,	See *supra* for all the elements of claim 1
wherein the composition is administered to the animal in a volume sufficient to deliver to the animal a dosage of cyphenothrin ranging from about 0.1 mg/kg to about 40 mg/kg.	These elements merely recite a dosage of the obvious composition. As discussed *supra*, the prior art disclosed dosages within this range: The dosage disclosed in the **'542 publication** is 0.24 mg/kg; The dosage disclosed in **the '510 patent** is 3 mg/kg. Further, see *supra* discussing the efficacy and duration data disclosed in the **EPA Report** that would render these claimed properties obvious to a POSA.

E. Any Secondary Considerations Fail to Overcome the Showing of Obviousness

While the Board should consider objective indicia of nonobviousness, such indicia do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). To the extent that the patent owner asserts any additional objective indicia in this proceeding, detailed consideration of such evidence should not be undertaken until Petitioner has had an opportunity to respond. *Amneal Pharm., LLC v. Supernus Pharm., Inc.*, IPR2013-00368 [Paper 8, pp. 12-13].

a) Patent Owner Cannot Merely Rely on Ex Parte Declaration Evidence Submitted During Prosecution

During prosecution of the '244 patent, patent owner submitted voluminous

charts and data along with inventor declarations purporting to show unexpected results. Patent owner cannot rely on the alleged data in any of these declarations in the present proceeding without first providing a declaration from a person who is familiar with the experiments, describing how the test was performed and the data was generated, which subjects the declarant to cross-examination in the present proceeding. Patent owner's reliance on data from *ex parte* declarations is barred by 42 C.F.R. § 42.65(b).

To the extent that the Board places any reliance on patent owner's declaration and data as presented during prosecution, the petitioner provides the following discussion showing that a POSA would understand that the claimed methods do not show any unexpected properties.

b) Declaration with Regard to Efficacy Data

During prosecution of the '244 patent, the patent owner alleged that because the concentration of cyphenothrin is less than 20% (w/w), the claimed methods exhibited unexpected efficacy and duration in light of the patent owner's allegation that such a low concentration of cyphenothrin would be expected to quickly degrade in the environment. Accompanying the Declaration of inventor Larry Nouvel, filed May 15, 2013, are five exhibits. As Dr. Clark opines, each exhibit has significant shortcomings and, as a result, the patent owner's conclusions with respect to the exhibits is untenable. (EX1002, ¶¶129-168). Further, only one of

the exhibits, Exhibit 5 even concerns the combination of fipronil and cyphenothrin. Thus, with respect to Exhibits 1-4, while these purport to establish what patent owner alleges a POSA might expect with respect to the activity of cyphenothrin over the relevant time period of around 4 weeks after administration, each is irrelevant to the issues here at least because none of them take into account the effect of fipronil. Notwithstanding the lack of relevance, for completeness, each exhibit is discussed in turn below.

In **Exhibit 1**, the patent owner conflates the two distinct concepts of dosage and concentration. Exhibit 1 is a graph showing the dosage (mg/kg body weight) of cyphenothrin versus duration of efficacy that purports to show what the patent owner alleged is a "positive relation between dosage (mg/kg) of cyphenothrin and duration of efficacy." (EX1003, pp. 228-229, Nouvel Declaration I, at pp. 1-2, ¶6, and its accompanying Exhibit 1). Exhibit 1 shows a linear regression that purports to be a predictive model of cyphenothrin's expected behavior. The patent owner concluded from Exhibit 1 that one wishing "to develop a composition containing cyphenothrin as a component that could maintain increased efficacy for a period of about four weeks (30 days) would not be motivated to use a concentration less than 20%, since duration would be predicted to only be one to two weeks at most." (EX1003, p. 229, Nouvel Declaration I, at p. 2, ¶6).

A POSA, however, would recognize that the patent owner conflates dosage

(mg active/kg body weight) and concentration (percentage of active in a volume of solvent). (EX1002, ¶131). Because the data in Exhibit 1 report on dosages, and dosage refers to the amount of active agent per weight of the animal, the data cannot provide any information about the concentration. (*Id*.). As such, any conclusion about concentration is "wholly unsupported." (*Id*., ¶134). Furthermore, as explained by Dr. Clark, the patent owner's own data reported in the EPA Report is inconsistent with the model the patent owner puts forth in Exhibit 1. (*Id*.). Moreover, the patent owner failed to provide a data source for the points drawn in the graph, and there is no explanation for the linear regression equation therein. (*Id*.). As such Exhibit 1 should carry no weight.

Exhibit 2 is a voluminous set of tables that purports to show the efficacy of 20% and 30% cyphenothrin *concentrations* against fleas and ticks on dogs. (*Id*. ¶135). Exhibit 2 relates to compositions wherein cyphenothrin is the only active, and therefore, does not take into account the effect of fipronil, a potent parasiticide. The patent owner alleged that "Exhibit 2 further supports my statement that the lower the *dosage* of cyphenothrin applied to a dog, a shorter duration of efficacy (at 95% or greater) will be observed." (EX1003, p. 229, Nouvel Declaration I, at p. 2, ¶7) (emphasis added). In his Declaration, Dr. Clark provides a detailed analysis of Exhibit 2, including considering factors such as fluctuating dosages within test groups that are not standard practice in this field (*id*.); the lack of

statistical significance of the data at the relevant time period, i.e., 3-4 weeks *(id*.); insufficient data from which the patent owner can reasonably draw its conclusion (*id*., ¶138); and that there is no practical difference in efficacy between any of the treatment groups despite the approximately two-fold difference in dose rate being applied across the groups (*id*.). All of this substantially detracts from the conclusion proffered by the patent owner.

In Exhibit 2, there are five groups of dogs (Groups A (control) and cyphenothrin treated groups B1-B4). From his analysis, Dr. Clark opines, that a constant dosage should be used in each treatment group, but only one group, Group B4 received a constant dosage, and that dosage is reported to be 25 mg/kg. (EX1002, ¶136). Even in light of the fluctuating dosages, the patent owner attempted to compare the activities between all the groups. In doing so, the patent owner alleged that there were "several statistically significant differences in flea and tick counts between groups of treated dogs, mostly that group B4 dogs treated at a minimum dose rate of 25 mg/kg had, on eight occasions, higher flea and tick counts than the other treated groups ($p<0.05$)" (EX1003, p. 230, Nouvel Declaration I, at p. 3, ¶7).

However, Dr. Clark opines that a POSA would recognize that from all the efficacy data points in Tables 6.1 and 6.2 for groups (B1-B4) *after 16 days*, none of the differences is significant, except one. (EX1002, ¶137). To a POSA, a single

data point is not enough information from which to draw a conclusion especially in light of the fact that other data points show no statistical significance. (*Id*). Consequently, in the correct light, Exhibit 2 reports that after 16 days there is no practical difference in efficacy between any of the treatment groups despite the approximately two-fold difference in dose rate being applied across the groups. (*Id*., ¶¶137-138).

Exhibit 3 purports to be a "Dose Titration of a Cyphenothrin Squeeze-On" against adult cat fleas and brown dog ticks on dogs. In his declaration, Nouvel concludes that "only the group of dogs that were administered cyphenothrin at a dose rate exceeding 50 mg/kg (58 mg/kg) generated data that supports the *desired 4 week residual efficacy claim* against ticks but not against fleas." (EX1003, p. 230, Nouvel Declaration I, at p. 3, ¶8, and its accompanying Exhibit 3) (emphasis added). Yet, Exhibit 3 itself informs the POSA that with respect to ticks, there is no real difference at the *desired 4 weeks* because, "only on the 58th day was there a statistically significant difference in tick burdens between the dogs treated with 25mg/kg and those treated at 100 mg/kg ($P<0.05$)." (EX1003, p. 183, patent owner's Response dated May 15, 2013, Exhibit 3, at p. 6, ll. 11-15). Additionally, Dr. Clark discusses patent owner's Table 4.2, that shows that cyphenothrin at 25 and 96 mg/kg body weight at 28 days, i.e., 4 weeks, are *each* 100% effective, and therefore cannot be statistically different. (EX1002, ¶142).

Yet, from only these two dosages (25 and 96 mg/kg), the patent owner compiled a so-called "Duration of Efficacy Prediction against Ticks" for 19 other dosages. (EX1002, ¶143, referring to Table 4.4.2 of Exhibit 3). As quoted above, the patent owner refers to dosages that have the *desired 4 week residual efficacy claim*. However, in terms of the predicted duration of efficacy, Table 4.4.2 in Exhibit 3, itself reports: "the predicted values for the mg/kg-residual efficacy are clearly **unreliable**." (EX1002, ¶143) (emphasis added).

Still referring to Exhibit 3, but now turning to flea data, Table 3.2 reveals what a POSA would expect when administering very large differences in dosages (25 and 96 mg/kg cyphenothrin)—that the efficacy against fleas at four weeks' time is not the same, i.e., 72% versus 99%, respectively. (*Id*., ¶144). This difference in activity further weakens the patent owner's hypothesis and the alleged linear regression set forth in Exhibit 1, because there is no linear relationship. That is, a reduction of 75% in the dosage (amount of cyphenothrin/kg body weight; 25 versus 96) leads to only a 27% loss (99 versus 72) in efficacy against fleas after four weeks. To a POSA, Exhibit 3 contradicts the patent owner's conclusion about its Exhibit 1. (*Id*.).

Exhibit 4 is simply a dosage escalation chart, and an apparent plan for a study. (*Id*., ¶145). It does not support any conclusion about Nouvel's tests. (*Id*).

Exhibit 5 is a study comparing a composition containing fipronil and

cyphenothrin against a composition containing fipronil alone. As discussed below, the study design is flawed because the patent owner changed two variables at once and did not account for these changes. (*Id*., ¶148). "In an effort to avoid the side effect of paraesthesia, I reduced the concentration of cyphenothrin to less than 20% *and* added a second active (fipronil), which was known to work well with cyphenothrin." (EX1003, Nouvel Declaration I, p. 4, ¶10, and its accompanying Exhibit 5) (emphasis added). Accordingly, in this study, the inventor "reduced" cyphenothrin while at the same time "added" fipronil. In doing so, any comparison on the four-week period of efficacy of the two compositions does not make scientific sense because cyphenothrin and fipronil are two different ectoparasiticides that act by different modes of action and speed of kill against fleas and ticks. Additionally, the study does not report a low-concentration cyphenothrin-only group. Without testing such a group, the data cannot report on the activity of low dose of cyphenothrin alone because the influence of fipronil cannot be separated from the overall efficacy of the combination. (EX1002, ¶148). It is therefore impossible to conclude any effect is tied to the lower concentration of cyphenothrin. (*Id*.).

The presence of fipronil would be expected to have a significant effect on the efficacy of the combined formulation because fipronil by itself is known to effectively control fleas and ticks for at least 30 days. (*Id*., ¶151; *see also* EX1010,

p. 397, last sentence). Indeed, as Dr. Clark opines, the patent owner's own data show this activity of fipronil in the Frontline Plus® formulation, i.e., "Group C" in Exhibit 5. (EX1002, ¶151). As can be seen from the data point at 29 days, fipronil by itself has 100% efficacy against fleas and 95% efficacy against ticks. (*Id*.). Fipronil also is shown to have a *level* of quick-kill activity. (*Id*., ¶152). Accordingly, the data show that the presence of fipronil affects the efficacy results of the test. (*Id*). And while there are statistical differences at some of the 1 and 4 hr post infestation time points for fleas and ticks in favor of the combination formulation over fipronil alone, this is entirely expected since the "quick-kill" property of cyphenothrin would be expected to add to the level of activity of fipronil at those early time points. (*Id*).

With respect to the data that are reported in Exhibit 5, Dr. Clark opines that while there are a few data points that appear to be statistically significant ($p<0.05$), at most time points there is no significant difference for fleas or ticks at the *desired 4 week duration*. (*Id*., ¶155). During prosecution, the patent owner alleged a significant difference "of fleas being killed at *all* tested points in time following initial application." (EX1003, p. 236, Nouvel Declaration I, at p. 6, ¶12). As Dr. Clark opines, for fleas, the 1 and 4 hr post infestation differences between the combination Group B and fipronil alone (Group C) are only significant up through Day 13. (EX1002, ¶155). For ticks, this difference appears only at the 1 hr post

infestation time points through Day 27, whereas for the 4 hr post infestation time points, only up to Day 6. (*Id*.). To a POSA, all of these results would be entirely expected because the formulation is a combination product that contains fipronil and cyphenothrin, the latter of which would be expected to add to the "quick-kill" activity of the formulation. (*Id*.). As such, a POSA would recognize that the differences between the B group and the C group in the raw data reflect an additive effect of the cyphenothrin in combination with fipronil. (*Id*., ¶¶160 and 163).

A POSA would have had a reasonable expectation of such an additive effect. With regard to fipronil, the data in the '542 publication show that fipronil-alone is working efficaciously for at least 37 days against adult fleas (100%) and against ticks (94%). (EX1004, pp. 29-30, Tables 2a, 2b and 3; *see also*, EX1002, ¶165). Exhibit 5, discussed above, shows that fipronil alone is killing ticks and fleas at day 27. Thus, the data show that, as expected, fipronil contributes substantially to the killing power of the composition throughout the length of the study conducted in Exhibit 5. (EX1002, ¶165).

As mentioned above, the patent owner's own p-values show that there is no significant difference in efficacy between fipronil only and the fipronil/cyphenothrin combination, and where there are differences this can be explained by the known quick-kill effect of cyphenothrin. (*Id*., ¶167). As such, Dr. Clark opines that the patent owner's hypothesis of an unexpected or surprising

beneficial effect of the combination should be rejected, and the alternative hypothesis that there is an expected additive effect should be accepted. (*Id*., ¶168).

c) Declaration with Regard to Cyphenothrin Stability

The stability of cyphenothrin once applied to an animal became an issue that patent owner stressed during prosecution and addressed with an inventor declaration by Larry Nouvel dated December 1, 2013 (hereinafter, "Nouvel Declaration II"). Specifically, the issue was whether cyphenothrin is stable enough to be expected to be present after three weeks to provide any so-called "quick-kill" activity. As discussed supra, cyphenothrin is an α-cyanopyrethroid, a class that possesses improved photostability. (EX1002, ¶170; *see also*, EX1011, p. 77, ll. 9-16). However, during prosecution, the patent owner alleged that the prior art: "clearly teaches that of all the pyrethroids, cyphenothrin is most unstable." (EX1003, p. 083, patent owner's Response dated October 1, 2013, at p. 11). Dr. Clark reviewed the art cited by the patent owner (Casas (2007); Fernández-Álvares (2007)), and concludes that the statements by the patent owner with respect to the teachings of the references are entirely speculative, simplistic and reflect a lack of understanding of the teachings. (EX1002, ¶¶176 and 184).

Casas (2007) (EX1012) relates to the study of the stability of pyrethroid-containing in water samples during storage, and is not analogous to the stability of a pyrethroid once it is applied as a spot-on composition to an animal. (EX1002,

¶173). The patent owner attempted to draw a correlation that because cyphenothrin was degraded relatively fast in a chlorinated tap water test (a phenomenon Casas dismissed as a "matrix effect"), the results are relevant because an animal is exposed to tap water "such as during a bath, while drinking, rain…" (EX1003, p. 084, patent owner's Response dated December 1, 2013, middle of p. 12). Plainly, rain is not made up of tap water. And while the patent owner deliberately directed the Examiner's attention to the tap water test, the other assays in Casas tell a different story. In a more real-world assay, Casas studied greenhouse runoff and found no decrease in response of the pyrethroids, including cypohenothrin. (EX1002, ¶176). In other assays, Casas teaches several water storage assays where cyphenothrin is more stable than cypermethrin, which is an α-cyanopyrethroid known to have a field life of greater than 20 days. (EX1013, p. 934, left column, Fig. 2; *see also*, EX1002, ¶¶173 and 174). As Dr. Clark concludes, Figures 2 and 3 of Casas show that cyphenothrin retained its chemical integrity as compared to several other species of pyrethroids, including cypermethrin. (EX1002, ¶¶174 and 1754). Indeed, Casas reaches a similar conclusion by stating: "Some of the most recently developed pyrethroids can persist in the environment for few months [sic] before they are degraded . . . ." (EX1012, p. 1841, right column; *see also*, EX1002, ¶¶178).

The authors of Fernández-Álvares (EX1014) intentionally degraded

pyrethroids at a single wavelength of UV irradiation. During prosecution, the patent owner did not mention the intentional degradation and wavelength selection, but argued that cyphenothrin degraded the quickest because it was the least stable. (EX1003, p. 083, patent owner's Response of October 1, 2013, p. 11, second full paragraph). Yet, Fernández-Álvares plainly informs the POSA that at the specific "working wavelength," i.e., 254 nm, "the faster photodegradation of cyphenothrin is consistent with its higher molar absorption coefficient at the working wavelength." (Fernández-Álvares, p. 239, sentence bridging to 1240; EX1002, ¶182). As such, Fernández-Álvares is not a teaching that cyphenothrin is the least stable in the environment. (EX1002, ¶¶ 183 and 185).

During prosecution, the patent owner alleged that Fernández-Álvares is relevant because an animal would be exposed to UV light from the sun and indoor lighting. According to Dr. Clark, a POSA would know that sunlight contains UV light in the form of a spectrum of wavelengths between 400 nm to 100 nm, and natural UV light at a single wavelength at a high intensity is never present in the environment as it was in the highly artificial test conditions. (*Id*., ¶185). As such, to a POSA, Fernández-Álvares does not show or even suggest that cyphenothrin is the most unstable pyrethroid in the real-world. (*Id*.).

VIII. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that Claims 1-22 of the '244 patent are unpatentable under 35 USC § 103 and respectfully requests that the Board so finds.

Dated: 25 March, 2016

Respectfully submitted,

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CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 25th day of March, 2016, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. 8,614,244, Power of Attorney, and all supporting exhibits were served via Federal Express to the Patent Owner, including by serving the correspondence address of record for the '244 patent:

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