UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Intervet Inc. a/k/a Merck Animal Health,
Petitioner

v.

Boehringer Ingelheim Vetmedica, Inc.,
Patent-Owner.

Case No. Unassigned

U.S. Patent No. 9,610,345

Petition for *Inter Partes* Review of U.S. Patent No. 9,610,345

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1006	Blanchard et al., *Protection of swine against post-weaning multisystemic wasting syndrome (PMWS) by porcine circovirus type 2 (PCV-2) proteins*, Vaccine 21:4565-4575 (2003) ("Blanchard")
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Petitioner's Exhibit No.	Document
1078	U.S. Patent No. 5,213,795
1079	U.S. Patent No. 9,011,872

I. INTRODUCTION

Intervet Inc. ("Petitioner") hereby petitions for *inter partes* review ("IPR"), asking the Board to cancel all claims of U.S. Patent No. 9,610,345 ("the '345 Patent," Ex.1001) because they are unpatentable under 35 U.S.C. §§ 102 and 103.

The '345 Patent claims methods of preventing and/or reducing one or more symptoms associated with infection by a particular porcine virus (PCV2) comprising the administration of a single dose of an immunogenic composition comprising a particular protein (ORF2) from PCV2 to piglets that are 2-6 weeks of age. The prior art teaches these same compositions and methods, as well as the protective effect against symptoms of PCV2 infection that they provide. To the extent Patent-Owner argues that the claims require, and that it was the first to recognize, that these prior art compositions could be effective in a single dose, even if this were correct, it is black letter law that recognizing and claiming an inherent property (*i.e.*, the protective effect provided by the claimed compositions and methods) does not render these old compositions and methods patentable. And even if claiming an inherent property of a known composition were enough to escape anticipation (and precedent makes clear that it is not), it would have been obvious to try a single dose

of the prior art compositions and there are ample teachings and data in the prior art to provide a reasonable expectation of success in doing so.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8, Petitioner provides the following mandatory disclosures:

A. REAL PARTIES-IN-INTEREST

The real parties-in-interest are Intervet International, B.V., Wim de Körverstraat 35, Boxmeer, 5831 AN, Netherlands; Intervet, Inc., 2 Giralda Farms, Madison, New Jersey 07940; and their parent company, Merck & Co., Inc., 2000 Galloping Hill Rd, Kenilworth, NJ 07033.

B. RELATED MATTERS

The ’345 Patent that is the subject of this IPR petition is also the subject of a patent litigation suit brought by Patent-Owner against Petitioner on May 21, 2018, *Boehringer Ingelheim Vetmedica, Inc. v. Merck & Co., Inc. and Intervet Inc. a/k/a Merck Animal Health*, Case No. 2:18-cv-09534-JMV-JBC (D.N.J.). Ex.1002. In the same litigation, Petitioner has asserted a counterclaim of infringement of Petitioner’s U.S. Patent No. 8,008,001 (“the ’001 Patent”) against Patent-Owner. Patent-Owner has filed a petition for IPR of the ’001 Patent (IPR2018-00919) in

which it makes various representations regarding the prior art asserted in this petition that are relevant to Petitioner's grounds herein. The Board has denied institution of that petition under 35 U.S.C. § 325(d). IPR2018-00919, Paper No. 13.

Petitioner has also filed two petitions for IPR of Patent-Owner's U.S. Patent No. 9,011,872 ("the '872 Patent"), which were accepted on October 22, 2018. IPR2018-01788 and -01789. In addition, Petitioner is concurrently filing a petition for IPR of Patent-Owner's related U.S. Patent No. 9,669,087 ("the '087 Patent"). Both of these patents are also at issue in the above litigation.

Finally, Petitioner notes that the European counterpart of the '345 Patent, EP2371382, was revoked by the Opposition Division of the European Patent Office on September 8, 2018. Ex.1056. The Division found that because the claims there were open-ended (as they are for the '345 Patent here), those claims do not preclude additional administration of other compositions that do not include ORF2 protein, and thus, the claims lack novelty over Blanchard and Jestin. Two other European counterparts to the '345 Patent, EP2371383 and EP2371385, were also revoked in September 2018. Ex.1056.

C. LEAD AND BACK-UP COUNSEL

Pursuant to 37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), and 42.10(a), Petitioner provides the following designation of counsel:

Lead Counsel	Back-up Counsel
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A Power of Attorney accompanies this petition in accordance with 37 C.F.R. § 42.10(b). Service via hand delivery or postal mail may be made at the addresses of the lead and back-up counsel above. Petitioner hereby consents to electronic service, and service via electronic mail may be made at the email addresses provided above for the lead and back-up counsel.

III. PAYMENT OF FEES

Pursuant to 37 C.F.R. §§ 42.103 and 42.15(a), $42,500 is being paid via deposit account 501408. Any additional fees due in connection with this petition may be charged to the foregoing account.

IV. STANDING

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '345 Patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR of the claims on the grounds identified herein.

V. IDENTIFICATION OF CHALLENGE AND STATEMENT OF PRECISE RELIEF REQUESTED

Petitioner requests that IPR be instituted on all claims (claims 1-30) of the '345 Patent based on the grounds below and that the Board issue an order cancelling those claims as unpatentable in light of the same.

A. GROUNDS

- GROUND 1: Claims 1-3, 5-12, 14-23, and 25-30 are anticipated under §102(b) by Blanchard;
- GROUND 2: Claims 1-3, 5-12, 14-23, and 25-30 are anticipated under §102(b) by Jestin;
- GROUND 3: Claims 1-3, 5-12, 14-23, and 25-30 are obvious under §103(a) over Blanchard in view of the knowledge of a POSA, and also in view of Jestin, Meng, and/or Fenaux;
- GROUND 4: Claims 4, 13, and 24 are obvious under §103(a) over Blanchard and/or Jestin, in view of the knowledge of a POSA, and also in view of Halbur and Thomas;
- GROUND 5: Claims 1-2, 4-11, 13-22, and 24-30 are anticipated under §102(b) over Halbur;
- GROUND 6: Claims 1-2, 4-11, 13-22, and 24-30 are obvious under §103(a) over Halbur in view of the knowledge of a POSA, and also in view of Fenaux and Thomas.

The Declarations of Darin Madson, D.V.M., Ph.D., an expert in veterinary medicine and porcine circovirus (Ex.1003), and Sylvia D. Hall-Ellis, an expert in library science (Ex.1068), accompany this petition.

B. PRIORITY DATE

The ’345 Patent issued from Application No. 15/249,158 (“the ’158 Application”), filed on August 26, 2016, which claims priority through a series of

applications to Provisional Application Nos. 60/755,016 and 60/829,809, filed December 29, 2005 and October 17, 2006, respectively. Ex.1001. Petitioner does not believe the '345 Patent claims are entitled to the benefit of these two Provisional Applications, but because the references in the grounds herein predate that application, the '345 Patent claims are invalid regardless.

VI. BACKGROUND

A. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art in December 2005 ("POSA") would have a doctorate of veterinary medicine (D.V.M.) (or an equivalent education or practical experience), or a Ph.D. (or an equivalent education or practical experience) in immunology, vaccinology, virology, animal science and/or husbandry, or a closely related field. A POSA would also have a general understanding of vaccine science, including veterinary vaccines. The knowledge may come from a POSA's training, experience, or thorough research and collaboration with other individual(s), e.g., as members of a research team or group. Ex.1003 ¶142.

B. SCOPE AND CONTENT OF THE ART BEFORE DECEMBER 2005

1. Immunology

Immunology is the study of the immune system, which is our body's defense mechanism against foreign agents like viruses and bacteria. Ex.1003 ¶20. The reaction to these foreign agents, or "pathogens," is called an immune response. Ex.1003 ¶21.

Immune responses may be innate or adaptive. Ex.1003 ¶22. Innate immune responses are rapid and not specific to particular foreign molecules. Ex.1003 ¶23. Adaptive immune responses are learned responses that occur after exposure to a specific foreign molecule. Ex.1003 ¶24. An antigen (specifically, an immunogen) is a molecule that induces this type of immune response. Ex.1003 ¶25. The adaptive immune system is capable of generating immunological "memory" to an antigen such that the immune response becomes more powerful against subsequent exposures to the same antigen. Ex.1003 ¶27.

A common immune response is the development of antibodies. Antibodies are Y-shaped proteins that bind to antigens. Ex.1003 ¶28. "Neutralizing" antibodies defend against attack by a pathogen by binding to the pathogen and inhibiting its biological effects. Ex.1003 ¶¶29-31.

2. Vaccinology

Vaccinology is the science of vaccines and vaccination. Ex.1003 ¶32. Vaccination is administration of an immunogenic composition to stimulate the body's adaptive immune response and generate immunological memory to protect against a particular pathogen. Ex.1003 ¶¶33-34. According to the '345 Patent, an "immunogenic composition can induce, stimulate or enhance the immune response against PCV2." Ex.1001 at 5:53-54; Ex.1003 ¶35. In this context, the antigen resembles some aspect of the pathogen, e.g., a protein from the exterior of the pathogen. Ex.1003 ¶36. The vaccine is designed such that it does not cause natural disease because it is either incapable of replicating or its live component is weakened. Ex.1003 ¶37. The antigen stimulates the adaptive immune system to generate antibodies, including neutralizing antibodies, which defend the body from attack by pathogens. Ex.1003 ¶38.

Should the vaccinated animal later encounter the actual pathogen, the animal's adaptive immune system can easily and quickly recognize the pathogen and generate the appropriate antibodies to defend against it. Ex.1003 ¶39. This provides a protective effect against infection by the pathogen and the clinical symptoms associated with the disease. Ex.1003 ¶39.

Vaccine efficacy (or protection) may be assessed by evaluating a subject's response (for example, clinical symptoms) after viral "challenge" and by testing for seroconversion induced by vaccination. Ex.1003 ¶40. To challenge a subject means to infect the subject with a known pathogen. Ex.1003 ¶41. Seroconversion is when pathogen-specific antibodies become detectable in the subject. Ex.1003 ¶42.

There are several types of vaccines. **Live, attenuated vaccines** use viruses with weakened pathogenicity, as the antigen. **Inactivated vaccines** use a "killed" pathogen that has been inactivated and therefore cannot result in infection. **Subunit vaccines** contain an antigenic portion of the pathogen, *e.g.*, antigenic proteins or fragments thereof, that is not itself infectious. **DNA vaccines** contain DNA that codes for an antigenic protein, which is produced when the DNA is taken up by cells. Ex.1003 ¶¶43-44. Virus-like particles (VLPs) may be used as a component of a subunit vaccine that mimics the structure of actual virus particles. Ex.1003 ¶¶45-47.

Vaccines may be administered in different regimens, called "protocols." In a single-dose regimen, the vaccine is administered once in an amount sufficient to confer protection against the disease. Ex.1003 ¶48. In the animal health field, single-dose vaccines are generally preferred due to price, efficiency and ease of

deployment. Ex.1003 ¶51. In a two-dose regimen like a prime-boost regimen, an initial "prime" dose of a vaccine is given, followed by a subsequent administration of the same or different vaccine re-exposing the patient to the same immunogen. Ex.1003 ¶49. A purpose of the booster dose is to enhance immunity against the immunogen. Ex.1003 ¶49.

Finally, vaccines typically contain one or more adjuvants, which help create a stronger immune response. Ex.1003 ¶¶52-53. They also commonly include a carrier and/or a pharmaceutically acceptable salt. Ex.1003 ¶54.

3. Use of Recombinant DNA Technology in Vaccine Development

Recombinant DNA technology was developed in the early 1970s, and has been used extensively in vaccine development. Ex.1003 ¶¶55-56. Recombinant DNA technology allows DNA segments from multiple species to be combined into a single "recombinant" DNA molecule. Ex.1003 ¶57. The recombinant DNA is introduced into cells from other living organisms, or host cells, which cells can then "express," i.e., produce, the protein(s) encoded by the recombinant DNA. Ex.1003 ¶58. These protein production systems are referred to as expression systems, and proteins that result from the expression of recombinant DNA are called recombinant proteins. Ex.1003 ¶58.

Baculoviruses are a family of insect viruses that are widely used for the production of recombinant proteins. Ex.1003 ¶59. As of December 2005, the baculovirus expression system was a powerful tool in the production of immunogenic proteins for use in vaccines. Ex.1003 ¶60.

4. Porcine Circovirus and Post-Weaning Multisystemic Wasting Syndrome

Porcine circovirus ("PCV") is a common virus in pigs. Ex.1003 ¶61. As of 2005, at least two PCV variants had been identified: type-1 ("PCV1"), which is non-pathogenic, and type-2 ("PCV2"). Ex.1003 ¶¶62-63. PCV2 was known to be associated with post-weaning multisystemic wasting syndrome (PMWS), a disease affecting weaning piglets. Ex.1003 ¶64. PMWS was first identified in 1991 in Canada, and reported in 1997; PCV2 was found to be associated with PMWS soon afterwards. Ex.1003 ¶65. Symptoms of PMWS include progressive weight loss, lung lesions, fever, anemia, jaundice, nasal shedding, diarrhea, coughing, dyspnea, and tachypnea. Ex.1003 ¶¶66-70.

PCV2 has a small, circular single-stranded genome encased within a protein shell called a "capsid." Ex.1003 ¶71. PCV2's genome has at least two major open reading frames (ORFs): ORF1 and ORF2. Ex.1003 ¶72. An ORF is a segment of

DNA that can be translated into a protein. Ex.1003 ¶73. In the PCV2 genome, ORF1 codes for the nonstructural "replicase" proteins, which allow the PCV2 virus to replicate. Ex.1003 ¶73. ORF2 codes for PCV2's only structural protein, the capsid protein, referred to herein as the ORF2 protein. Ex.1003 ¶74.

5. PCV2 Vaccines

As of December 2005, it was known that the ORF2 protein is the primary immunogenic protein for PCV2, and thus a POSA had strong motivation to create vaccines containing the ORF2 protein. Ex.1003 ¶¶75-76; Ex.1009 at 5. Indeed, Patent-Owner's '872 Patent, which predates the '345 Patent, acknowledges that vaccines using ORF2 proteins were already known in the art. Ex.1079 at 2:22-25 ("[the] (ORF2) protein of PCV2 … has been utilized in the past as an antigenic component in vaccines for PCV2"); Ex.1003 ¶77. As of December 2005, several types of PCV2 vaccines using ORF2 proteins had been developed and were known to be effective, including both recombinant live and inactivated virus and subunit vaccines. Ex.1003 ¶78.

Meng teaches three types of vaccines that code for, or express, recombinant ORF2 protein as their antigenic component: subunit vaccines, DNA vector vaccines,

and live and inactivated chimeric PCV1-2 virus vaccines.[1] Ex.1003 ¶¶85-92. Fenaux continued the work reported in Meng, describing experiments with a live chimeric PCV1-2 virus vaccine that includes the recombinant PCV2 ORF2 protein. Ex.1003 ¶¶93-99. As discussed in more detail below, Fenaux's PCV1-2 virus vaccine was shown to provide a protective effect against clinical symptoms associated with PCV2 infection after a single dose. Halbur, another follow-up to the work in Meng, also showed that a single dose of the PCV1-2 virus administered to 3-week-old piglets provided such a protective effect. Ex.1003 ¶¶100-101. Other references, like Thomas and Bublot, also taught the administration of PCV2 vaccines to piglets at about three weeks of age—a time when piglets are commonly weaned and any maternally derived immunity to PCV2 infection begins to fade. Ex.1003 ¶¶349-352.

Jestin and Blanchard describe subunit vaccines containing recombinant ORF2 protein as their antigenic component. Ex.1003 ¶¶102-118. As discussed in more detail below, Jestin discloses the administration of a single dose of a subunit vaccine

[1] The chimeric PCV1-2 vaccine is a "chimera" that contains the ORF2 capsid protein from PCV2 and the replicase proteins from PCV1.

containing an effective amount of the ORF2 protein to 5-week-old piglets. Blanchard discloses data showing that its ORF2 subunit vaccine provides a protective effect against symptoms of PCV2 infection after a single dose to 5-week-old pigs and 4-week-old pigs in Trials 1 and 2, respectively.

In addition, as of December 2005, other researchers, for example Parisot and Reynaud, were studying the efficacy of single-dose vaccines containing inactivated PCV2 virus, and thus ORF2 protein. Ex.1003 ¶¶79-84. Thus, at that time, researchers were developing PCV2 vaccines containing ORF2 protein in both single-dose and prime-boost regimens. Ex.1003 ¶78.

C. THE '345 PATENT

The claims of the '345 Patent are directed to methods for preventing and/or reducing one or more symptoms of PCV2 infection by administering a single efficacious dose of an immunogenic composition comprising PCV2 ORF2 protein to piglets 2 to 6 weeks of age. Ex.1001; Ex.1003 ¶119-121. It has three independent method claims: claims 1, 10, and 20. Ex.1003 ¶120. Claim 1 is directed to a method of preventing or reducing symptoms of PCV2 infection comprising administering a single dose of the claimed immunogenic composition and an additional component like an adjuvant. Ex.1003 ¶121.

Claim 10 is directed to a method of preventing or reducing certain symptoms of PCV2 infection comprising administering a single dose of the claimed immunogenic composition. Ex.1003 ¶121. Claim 20 is directed to a method of providing a protective effect against symptoms of PCV2 infection comprising administering a single dose of the claimed immunogenic composition. Ex.1003 ¶121.

As detailed below, Jestin and Blanchard each teach every element of claims 1-3, 5-12, 14-23, and 25-30 of the '345 patent, and Halbur teaches every element of 1-2, 4-11, 13-22, and 24-30 of the '345 Patent. Those claims are also obvious in light of the same references and in further view of Meng, Fenaux, and Thomas. To the extent any element is not explicitly discussed in these references, it is a routine aspect of vaccine development that would have been well known to a POSA.

D. PROSECUTION HISTORY AND SECTION 325(D)

The Examiner did not consider the same, nor any substantially similar, grounds to those presented in this Petition during prosecution. First, none of the relevant disclosure of the references in the grounds herein was explicitly considered during prosecution. *See generally* Ex.1003 ¶¶145-149. The primary references in

the grounds herein are Blanchard, Jestin, and Halbur. The Examiner did not rely on Blanchard, Jestin, or Halbur as the basis for any rejection.

Second, the Petition relies on additional evidence that was not before the Examiner, including Patent-Owner's admissions in a subsequently filed IPR petition (Ex.1009), testimony from Patent-Owner's declarant demonstrating that Blanchard's and Jestin's vaccines comprise effective amounts of recombinant ORF2 protein according to the '345 Patent (Ex.1010), and the expert testimony submitted by Petitioner here (Ex.1003).

Even for those references that are cited on the face of the '345 Patent, the Petition cites disclosures that were not expressly considered during prosecution and explains not only why these disclosures would have provided a POSA with a reasonable expectation that a single dose of those vaccines administered to piglets at 2-6 weeks of age would provide a protective effect against clinical symptoms associated with PCV2, but also why such disclosures show that a single dose *did* provide that protective effect. *See supra* Sections VII.B-G. There is nothing to suggest that the Examiner considered, much less appreciated the impact of, this evidence.

Third, this Petition presents legal arguments that were not previously addressed. The Examiner did not consider the law of inherency as it applies to the "preventing and/or reducing," "protective effect," and "single efficacious dose" language. The prior art in the grounds herein describes the same compositions claimed in the '345 Patent, i.e., vaccines comprising PCV2 ORF2 protein and an additional component like an adjuvant, and teaches how to make and to administer a single dose to piglets when they are 2-6 weeks of age. Even if Patent-Owner was the first to recognize that such compositions could provide a protective effect after a single dose (it was not), the recognition of that inherent property does not confer patentability on its claims. Section VII.A.1. Nor must the prior art recognize that inherent property, for example, with data showing efficacy after a single dose, for it to be enabled as an anticipatory reference, so long as protective effect necessarily occurs after a single dose. *Id.*

Therefore, the grounds here are not the same, nor are they substantially the same, as the arguments considered during prosecution and any argument for non-institution under 35 U.S.C. § 325(d) is misplaced.

E. CLAIM CONSTRUCTION

At least the following terms require construction:

1. ***"A method … comprising administering … a single efficacious dose of an immunogenic composition comprising PCV2 ORF2 protein"* (claims 1, 10, 20)**

The claims of the '345 patent use "comprising" as their transitional phrase. This means that they do not exclude additional steps, including the administration of other compositions before, after, or concurrently with the recited "administering" step. While the claims are limited to a "single efficacious dose" of an immunogenic composition comprising PCV2 ORF2 protein (claims 1, 10, 20), they do not preclude additional steps in which compositions that do not contain ORF2 protein are administered. Accordingly, the claims encompass vaccine protocols comprising multiple injections at different intervals so long as only one of those doses contains an immunogenic composition comprising PCV2 ORF2 protein.

2. ***"preventing and/or reducing one or more symptoms of PCV2 infection"* (claim 1); *and "aiding in the prevention and/or reduction of one or more symptoms caused by PCV2 infection"* (claim 10); *"providing a protective effect against one or more symptoms of porcine circovirus type 2 (PCV2) infection"* (claim 20)**

The "preventing and/or reducing" element in the preamble of claim 1 encompasses "eliciting or enhancing an immune response" that results in a reduction in the incidence of, severity of, or prevention of one or more of the symptoms

associated with PCV2 infection. Ex.1001 at 5:53-55, 7:18-20; Ex.1003 ¶¶127,129. Similarly, the phrase "aiding in the prevention and/or reduction" and the phrase "providing a protective effect" in the preambles of claims 10 and 20, respectively, encompass "eliciting or enhancing an immune response" that results in the prevention and reduction of one or more symptoms associated with PCV2 infection. Ex.1001 at 5:53-55, 7:18-20; Ex.1003 ¶¶127,129.

Moreover, such reduction, prevention, and/or protective effects can be of any magnitude, duration, or type; and 100% efficacy is not required. For example, according to data in the '345 Patent, clinical symptoms were still observed in about 10% or more of the piglets vaccinated in the patent examples. Ex.1001 at 27:25-28:14 (reporting that 8.3% of vaccinated pigs exhibited nasal shedding, and 16.7% had at least one tissue positive for PCV2); Ex.1003 ¶128.

VII. GROUNDS FOR UNPATENTABILITY

A. LEGAL STANDARDS

1. Anticipation

To anticipate a claim, a single prior art reference must disclose every limitation of the claimed invention either expressly or inherently. *HTC Corp. v. Cellular Commc'ns Equip., LLC*, 877 F.3d 1361, 1368 (Fed. Cir. 2017). "[A] prior

art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Inherent anticipation is particularly applicable to later-discovered properties of previously known processes and compositions.

Indeed, "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("*BMS*") ("Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent."); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44 (Fed. Cir. 2005). Here, as in *BMS*, Patent-Owner has done no more than claim a result (protective effect against clinical symptoms associated with a PCV2 infection) of a single dose of a known immunogenic composition (one containing ORF2 protein), with the same purpose as those known immunogenic compositions, to protect against PCV2 infection. This claim element cannot impart novelty. *See also In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir.

2012) ("[W]e agree with the Board that even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps."); *Application of May*, 475 F.2d 1082, 1090 (C.C.P.A. 1978).

"[I]nherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Schering*, 339 F.3d at 1377; *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

Furthermore, "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005). In *Rasmusson*, the Federal Circuit, considering the validity of a method of treating prostate cancer by administering finasteride, reversed the Board's determination that a prior art patent lacked an enabling disclosure because it failed to demonstrate that finasteride is effective in treating prostate cancer. *Id.* In doing so, the court reaffirmed the holding in *BMS* that "'anticipation does not require actual performance of suggestions in a

disclosure,'" and even that "a reference is no less anticipatory if, after disclosing the invention, the reference then disparages it." *Id.* (quoting *BMS*, 246 F.3d at 1376, 1378). In *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, the Federal Circuit explained that "[w]hile section 112 'provides that the specification must enable one skilled in the art to "use" the invention,' . . . 'section 102 makes no such requirement as to an anticipatory disclosure . . . .'" 424 F.3d 1347, 1355 (Fed. Cir. 2005). Rather, "[t]he critical inquiry" for anticipation is simply whether the prior art enables a POSA to make the claimed composition or carry out the claimed method steps. *Id.*

2. Obviousness

A patent claim is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103.

Of particular relevance is Federal Circuit precedent holding that claims to a dosing regimen are obvious where that regimen, *e.g.*, a single dose as opposed to two doses, was obvious to try and the evidence established a reasonable expectation of success. *See, e.g.*, *AstraZeneca LP v. Breath Ltd.*, 542 F. App'x 971, 979-80 (Fed. Cir. 2013) (holding invalid as obvious a patent relating to a once-daily asthma

treatment where an inherent property of the drug made it attractive to once-daily dosing and the evidence established a reasonable expectation of success); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331-32 (Fed. Cir. 2014) (holding that "[a]t the very least," a monthly dosing regimen for the treatment of osteoporosis would have been "obvious to try," and stating that "[c]onclusive proof of efficacy is not necessary to show obviousness").

B. GROUND 1: CLAIMS 1-3, 5-12, 14-23, AND 25-30 ARE ANTICIPATED BY BLANCHARD

Blanchard teaches a vaccine comprising recombinant PCV2 ORF2 protein produced from a baculovirus expression system. Ex.1003 ¶¶107, 111. The authors evaluated "the efficacy of protection induced by" that vaccine "by growth parameters and clinical signs, such as fever, compared to non-vaccinated and challenged piglets." Ex.1006 at 4566; Ex.1003 ¶107.

In Trial 1, Blanchard administered DNA vaccines comprising plasmids encoding the ORF1 or ORF2 protein to piglets, and two weeks later the same DNA vaccines plus a protein vaccine containing the PCV2 ORF2 protein, either by itself ("Orf2-vaccine group") or in combination with the ORF1 protein ("Orf1&Orf2-vaccine group"). Ex.1003 ¶109. The DNA vaccines comprised only DNA, so only

a single dose of a composition comprising the recombinant PCV2 ORF2 protein was administered. *Id.* As discussed *supra* Section VI.E.1, the claims of the '345 Patent are open-ended and thus do not preclude the earlier and concurrent administrations of the DNA vaccine. Based on the data from Trial 1, Blanchard concluded that the recombinant ORF2 protein, as opposed to ORF1, is the major immunogenic protein whose administration induces an immune response against the PCV2 virus. Ex.1003 ¶¶109-111. Moreover, Blanchard teaches that "no" clinical symptoms were observed after PCV2 challenge for those piglets that received the single dose of PCV2 ORF2 protein. Ex.1003 ¶110.

In Trial 2, Blanchard compared the efficacy of (i) a DNA vaccine containing both the ORF1 and ORF2 plasmids, and (ii) a protein subunit vaccine containing recombinant ORF1 and ORF2 proteins. Ex.1003 ¶¶112-113. While Blanchard ultimately administered two doses of the protein vaccine, the data in Blanchard show seroconversion after just the first dose of the ORF2 subunit vaccine administered to piglets at 28 days of age. Ex.1003 ¶114. The antibodies induced by that single dose were effective in neutralizing the PCV2 virus after challenge, suggesting that just a single dose of Blanchard's ORF2 protein vaccine would provide at least some degree of protective effect. Ex.1003 ¶¶114-118.

1. Claim 1

1.a. "A method for preventing and/or reducing one or more symptoms of PCV2 infection comprising"

Blanchard discloses a method of preventing and/or reducing one or more symptoms of PCV2 infection. As discussed further below, in Trials 1 and 2, piglets were administered a single dose of an ORF2 subunit vaccine that enhanced or elicited an immune response that conferred protection to prevent and/or reduce one or more symptoms after subsequent PCV2 challenge. Ex.1003 ¶157.

1.b. "administering to a piglet or group of piglets 2-6 weeks of age a single efficacious dose of an immunogenic composition comprising PCV2 ORF2 protein"

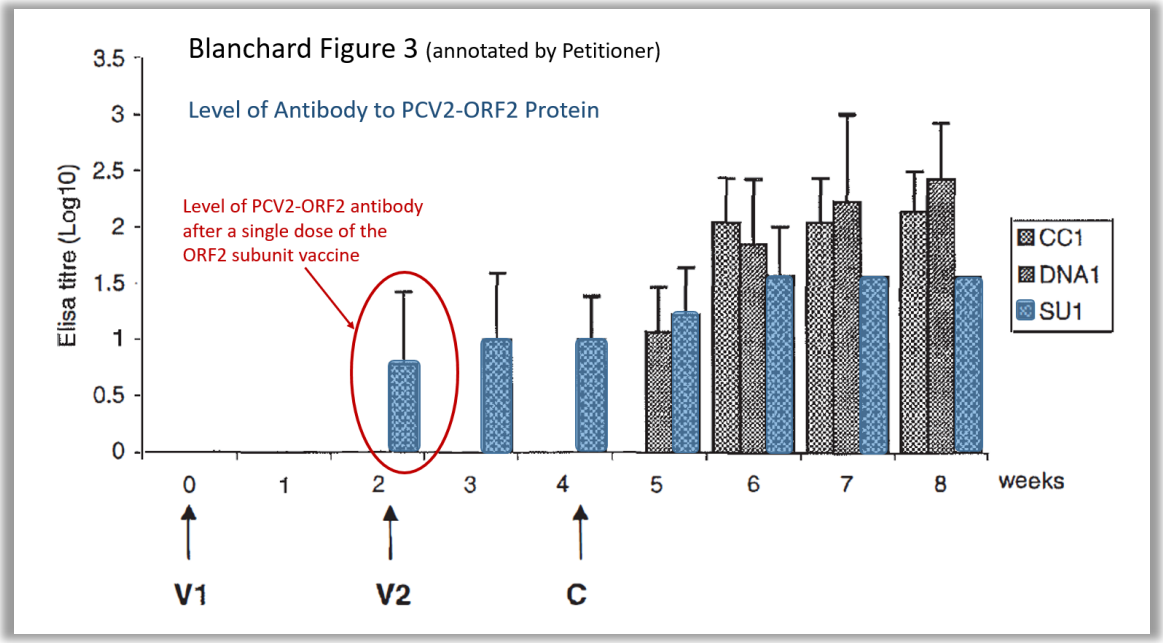
Blanchard teaches an immunogenic composition, *i.e.*, an ORF2 subunit vaccine that contains an antigen (ORF2 protein) and elicits or enhances an immune response. Ex.1003 ¶¶158-160. For example, Blanchard discloses that piglets developed antibodies to PCV2 ORF2 after a single dose of the vaccine, which is a classic immune response. Ex.1003 ¶¶160-162. The authors of Blanchard also "evaluate[d] the **immunogenic** and protective properties of PCV2-proteins" and "showed that the **Orf2-encoded capsid protein**, used in a preparation-based DNA and subunit vaccine, constitutes the major **immunogen** to induce protection of piglets against a PCV2 challenge." Ex.1006 at 4572, 4573; Ex.1003 ¶163.

Blanchard's immunogenic composition comprises recombinant PCV2 ORF2 protein. Ex.1003 ¶164. Blanchard's ORF2 subunit vaccines comprise PCV2 ORF2 protein expressed recombinantly in baculovirus, designated as "Orf2/PCV2 - 5 x 10^6 cells" in Tables 1 and 2. Ex.1006 at 4566-4577; Ex.1003 ¶¶165-166. Patent-Owner agrees that "Blanchard discusses injecting piglets with a PCV2 vaccine, including one comprised of the **ORF2 protein of PCV2**." Ex.1009 at 22; *see also* Ex.1016 ¶27 ("Blanchard et al., describes successful vaccination by administration of **ORF2 PCV2** produced by **recombinant baculovirus** in insect cells by methods standard at the time."); Ex.1003 ¶167.

Blanchard also teaches the administration of a single efficacious dose of an ORF2 protein vaccine to piglets between 2-6 weeks of age. In Trial 1, a single efficacious dose of the ORF2 subunit vaccine is administered at 39 days of age (*i.e.*, around 5.5 weeks). Ex.1003 ¶168. While Trial 1 also involved the administration of a DNA vaccine, the claims are "comprising" claims and do not exclude the administration of other non-ORF2 protein immunogenic compositions. *See supra* Section VI.E.1.

In Trial 2, the first dose of the ORF2 subunit vaccine was administered at 28 days of age (*i.e.*, 4 weeks). Ex.1003 ¶168. While a second dose was later

administered, Blanchard's data demonstrate that the first dose was alone sufficient to induce an immune response that generated a high level of PCV2-specific antibodies. Ex.1003 ¶¶172-181. Specifically, Figure 3 (annotated by Petitioner) below shows the levels of antibodies specific to PCV2 ORF2 protein induced by the recombinant ORF2 protein, i.e., seroconversion, over time in Trial 2 (blue bars). Ex.1003 ¶¶172-175. The data taken just prior to the second injection (V2) show that seroconversion was detected two weeks after administration of a single dose of Blanchard's ORF2 vaccine (V1). Ex.1003 ¶¶172-175. This is confirmed by Blanchard's statement that "[w]e obtained earlier **seroconversion with the subunit vaccine** 2 weeks **after the first injection**, at the time of the second injection." Ex.1006 at 4573; Ex.1003 ¶176.



Blanchard further indicates that the antibodies induced by the recombinant ORF2 protein were effective in neutralizing the PCV2 virus after challenge. Ex.1006 at 4573 ("These findings are in favor of better protection induced by the subunit vaccine, eliciting an **early antibody response able to neutralize the virus**."); Ex.1003 ¶180.

These results indicate that the first dose of Blanchard's ORF2 protein subunit vaccine induced the production of neutralizing antibodies. Ex.1003 ¶¶176-181. A neutralizing antibody is an antibody that defends a cell from an antigen (like the PCV2 virus) by neutralizing the biological effect of that antigen. Ex.1003 ¶29. In

order to protect against clinical symptoms associated with PCV2 infection, a sufficient level of neutralizing antibodies must be generated. Ex.1003 ¶178. Blanchard's ORF2 protein vaccine clearly demonstrates antibody production after a single dose, and the subunit vaccine ultimately completely prevented clinical symptoms associated with PMWS. Ex.1003 ¶179. Consequently, Blanchard states that "our results . . . tend to suggest that the subunit vaccine induced a Th2-like humoral response, based on **neutralizing antibodies**." Ex.1006 at 4573; Ex.1003 ¶180.

Further, Figure 3 shows that the antibody level induced by Blanchard's ORF2 subunit vaccine remained relatively constant from 14 days post-vaccination to after the second injection and after challenge. Ex.1003 ¶181. Indeed, the level of antibodies after the first injection was roughly the same level that was ultimately able to "provide significant protection against PCV2 infection" after two injections, indicating that the first dose of the ORF2 subunit vaccine provided a robust immune response that was similar to that seen after two injections. Ex.1006 at 4574; Ex.1003 ¶181. Thus, a POSA would understand from Figure 3 that just the first (single) dose of Blanchard's ORF2 protein vaccine in Trial 2 was inherently sufficient to prevent or reduce clinical symptoms. Ex.1003 ¶182.

While the prevention or reduction of clinical symptoms is inherent from the data showing the production of neutralizing antibodies, Blanchard also expressly teaches that its ORF2 protein subunit vaccine protected against clinical symptoms associated with PCV2 infection. Ex.1003 ¶183. Specifically, Table 3 of Blanchard sets forth the "[c]linical protection of vaccinated groups after PCV2 challenge in trial no. 1," *i.e.*, the trial in which a single dose of PCV2 ORF2 protein was administered following an initial injection of a DNA vaccine, and states that there were "**no**" clinical symptoms for piglets who received that single dose of ORF2 protein. Ex.1007 at 4569; Ex.1003 ¶183. In contrast, the piglets that did **not** receive that single dose of the ORF2 protein displayed a variety of clinical symptoms of PCV2 infection, including "dyspnea, tremor, ataxia, rough hair-coat, prostration" and in two instances more severe "wasting" that required the animal to be euthanized before the experiment was completed. Ex.1007 at 4568; Ex.1003 ¶183. Similar results were also seen in Trial 2, where the piglets receiving Blanchard's ORF2 protein vaccine likewise exhibited "No" clinical symptoms of PWMS after challenge. Ex.1006 at 4570; Ex.1003 ¶183. Thus, in both trials, Blanchard teaches that a single dose of an immunogenic composition comprising PCV2 ORF2 protein is sufficient to prevent or reduce clinical symptoms of PMWS and PCV2 infection.

Finally, this limitation is inherently disclosed because an ORF2 protein vaccine composition prepared according to the protocol in Blanchard contains a dose of ORF2 protein within the preferred dosage ranges taught in the '345 Patent. Ex.1003 ¶184. In a related proceeding, Patent-Owner submitted a declaration from its principal scientist, Dr. Schaeffer, stating that he made the ORF2 protein vaccine taught in Blanchard and determined that it contained recombinant ORF2 protein in an amount "between 106 and 169 μg/dose." Ex.1010 ¶¶2, 8; *see also* Ex.1009 at 22; Ex.1003 ¶¶184-185. The 106-169 μg/dose taught in Blanchard is significantly higher than the minimum effective dose of 0.2 μg/dose described in the '345 Patent. Ex.1001 at 10:14-21 (a concentration of ORF2 protein as low as 0.2 μg per dose is "effective for inducing the desired immune response, namely reducing the incidence of or **lessening the severity of clinical signs resulting from PCV2 infection**"); Ex.1003 ¶186. It is also within both the '345 Patent's preferable dose range of "0.2 to 400 μg/dose," and the narrower "more preferabl[e]" range of "0.3 to 300 μg/dose." *Id.* at 10:36-37; Ex.1003 ¶186. Thus, the single dose of the ORF2 protein vaccine administered in Trial 1, as well as initial dose given to the subunit-vaccine group in Trial 2, inherently anticipates this limitation because, according to the '345 Patent and Patent-Owner's declaration, the amount of PCV2 ORF2 protein in that

single dose was effective for preventing or reducing symptoms of PCV2 infection. Ex.1003 ¶187.

1.c. "and at least one additional component selected from the group consisting of a veterinary-acceptable carrier, a pharmaceutical-acceptable carrier, an adjuvant, cell culture supernatant, a preservative, a stabilizing agent, a viral vector, and an immunomodulatory agent."

Blanchard's ORF2 subunit vaccine also contains additional components selected from the claimed group, including a "viral vector," "adjuvant" and a "pharmaceutical-acceptable carrier." Ex.1003 ¶188. First, Blanchard discloses the use of "[t]wo recombinant baculoviruses," *i.e.*, viral vectors, containing the DNA for the ORF1 and ORF2 proteins. Ex.1006 at 4566; Ex.1003 ¶189. These baculoviruses are used to infect Sf9 cells, a type of insect cells, which then produce the ORF1 and ORF2 proteins. Ex.1003 ¶190. In order to release those proteins, the Sf9 "cells were **lysed** by freezing at -70 °C and thawing." Ex.1006 at 4566; Ex.1003 ¶191. This freeze-thaw cycle kills the Sf9 cells and inactivates at least some of the recombinant baculoviruses, producing inactivated viral vectors. Ex.1003 ¶192. Blanchard teaches that the ORF2 subunit vaccine is prepared from the lysate, *i.e.*, the fluid containing the contents of the lysed cells including these inactivated viral

vectors. Ex.1003 ¶193. Thus, Blanchard's ORF2 subunit vaccine contains an additional component consisting of a "viral vector." Ex.1003 ¶193.

Second, Blanchard teaches the addition of an adjuvant to its ORF2 protein subunit vaccine. Ex.1003 ¶194. Tables 1 and 2 show that the ORF2 subunit vaccines were injected with "Montanide," which Blanchard explains is a "**water-in-oil adjuvant**." Ex.1006 at 4567; *see also* Ex.1016 ¶26 ("The dose administered" in Blanchard included "Montanide which is a commercially available oil-in-water **adjuvant**."); Ex.1003 ¶¶194-195.

Third, Blanchard discloses a pharmaceutical-acceptable carrier in its ORF2 subunit vaccine. Ex.1003 ¶196. Blanchard teaches that "the protein vaccine was prepared" by completing "500 µl of crude lysate from each recombinant baculoviruses . . . to 1 ml of **PBS** pH 7.2." Ex.1006 at 4566; Ex.1003 ¶196. PBS, which stands for Phosphate Buffered Saline, is being used to dilute the 500 µL to a volume of 1 mL, and thus is a pharmaceutical-acceptable carrier as defined by the '345 Patent. Ex.1001 at 13:8-13; Ex.1003 ¶196.

2. Claim 2

"The method of claim 1, wherein said PCV2 ORF2 protein comprises a protein selected from the group consisting of:

a. a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11;

b. any polypeptide that is at least 90% homologous to the polypeptide of a);

c. a polypeptide that is encoded by a polynucleotide comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 4; or

d. any polypeptide that is encoded by a polynucleotide that is at least 90% homologous to the polynucleotide of c).”

The ORF2 protein in Blanchard’s ORF2 subunit vaccine meets this limitation. Ex.1003 ¶199. That protein is encoded by the polynucleotide sequence with GenBank Accession No. AF201311. Ex.1003 ¶199. According to BLAST®, the sequence comparison tool identified in the ’345 Patent (Ex.1001 at 8:21-30), the polynucleotide of GenBank Accession No. AF201311 is 97% identical to the polynucleotide sequence of SEQ ID No. 3 of the ’345 Patent, which is at least 90% homologous as set forth in element 2.d. Ex.1003 ¶¶197-202.

3. Claim 3

“The method of claim 1, wherein said PCV2 ORF2 protein is a recombinant baculovirus-expressed ORF2 protein.”

Blanchard’s ORF2 protein vaccine contains an inactivated recombinant baculovirus-expressed PCV2 ORF2 protein. Ex.1003 ¶203. In a section entitled “Production and characterization of **baculovirus-expressed proteins**,” Blanchard explains that “[t]wo recombinant baculoviruses were obtained” that contain the

DNA for the ORF1 and ORF2 proteins. Ex.1006 4566; Ex.1003 ¶¶204-205. These baculoviruses are used to infect Sf9 cells, a type of insect cells, which then produce the ORF1 and ORF2 protein. Ex.1003 ¶206. The proteins expressed by those cells are "baculovirus expressed ORF2 proteins." Ex.1003 ¶206. Patent-Owner agrees that "Blanchard et al., describes successful vaccination by administration of **ORF2 PCV2 produced by recombinant baculovirus** in insect cells by methods standard at the time." Ex.1016 ¶27; Ex.1003 ¶207.

4. Claim 5

"The method of claim 1, wherein the symptom is PCV2 virus shedding."

As discussed *supra* Claim 1, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including the symptom of virus shedding. Ex.1003 ¶¶208-214.

In addition, Blanchard teaches that its ORF2 protein vaccine induced an immune response that induced antibodies that were able to neutralize the PCV2 virus after challenge. These antibodies, by their nature, neutralize the virus, preventing replication and viremia and viral shedding. Ex.1003 ¶215. Indeed, the antibodies

completely prevented PCV2 DNA in tissue samples after two doses of the vaccine. Ex.1006 at 4571, Fig. 4; Ex.1003 ¶215. Blanchard's data show that the level of antibodies was roughly the same before and after the second dose. Ex.1003 ¶215. Accordingly, Blanchard also teaches that the administration of a single dose of ORF2 protein prevented virus shedding and viremia. *Id.*

5. Claim 6

"The method of claim 1, wherein the symptom is lymphoid infection caused by PCV2."

As discussed *supra* Claim 1, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including the symptom of lymphoid infection caused by PCV2. Ex.1003 ¶216.

In addition, Figure 4 from Trial 2 shows the detection of PCV2 DNA in various tissue samples, including bronchial, inguinal, and mesenteric **lymph nodes**. The results showed virtually no viral dissemination (*i.e.*, no virus shedding or lymphoid infection) and thus significant viral neutralization by the ORF2 subunit vaccine. Ex.1003 ¶217. While the results in Figure 4 were obtained after two doses

of Blanchard's ORF2 subunit vaccine, they nevertheless demonstrate the ORF2 subunit vaccine reduced and/or prevented the symptoms associated with PCV2 infection. Ex.1003 ¶217.

6. Claim 7

"The method of claim 1, wherein the symptom is increased mortality rate in a group of piglets."

As discussed *supra* Claim 1, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including the symptom of increased mortality rate caused by PCV2 in a group of piglets. Ex.1003 ¶218. Because Blanchard's single-dose ORF2 protein vaccine prevents PMWS, it therefore necessarily prevents symptoms of PMWS. Ex.1003 ¶219. And because Blanchard discloses that a single dose of its ORF2 protein vaccine prevented PMWS and symptoms thereof, it also discloses that that single dose prevented increased mortality rate associated with PMWS and the symptoms thereof. Ex.1003 ¶219.

7. Claim 8

"The method of claim 1, wherein the symptom is decreased average daily weight gain."

As discussed *supra* Claim 1, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including the symptom of decreased average daily weight gain caused by PCV2. Ex.1003 ¶220.

Blanchard also expressly teaches that its ORF2 protein vaccine prevented decreased average daily weight gain. Specifically, "[t]o evaluate clinical protection" in Trial 1, Blanchard "determined at ΔGW3 index, corresponding to the difference in mean daily weight gain . . . during the third-week post-challenge period between vaccinated pigs and challenge-control pigs (Table 3)." Ex.1006 at 4566; Ex.1003 ¶221. Table 3 shows that both the Orf2-vaccine and Orf1&Orf2-vaccine groups displayed significantly higher mean daily weight gains, *i.e.*, gaining "1.09" and "0.6" more % kilograms per day, respectively, as compared to the unvaccinated control group. Ex.1003 ¶222. Blanchard states that "[t]hese results confirmed a **significant enhancement of protection** after vaccination with an Orf2-based preparation (DNA and **recombinant protein**), confirming Orf2 as a major protective immunogen." Ex.1006 at 4568; Ex.1003 ¶223.

8. Claim 9

"The method of claim 1, wherein the symptom is PCV2 viremia."

As discussed *supra* Claim 1, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including the symptom of PCV2 viremia caused by PCV2. Ex.1003 ¶224.

In addition, as discussed *supra* Claim 5, Blanchard discloses that its ORF2 vaccine prevents and/or reduces PCV2 viremia. Ex.1003 ¶ 225.

9. Claim 10

10.a. "A method for aiding in the prevention and/or reduction of one or more symptoms caused by PCV2 infection comprising"

Blanchard in both Trial 1 and Trial 2 discloses a method of aiding in the prevention and/or reduction of one or more symptoms of PCV2 infection. *See supra* Claim 1; Ex.1003 ¶226.

10.b. "administering to a piglet or group of piglets 2 to 6 weeks of age a single efficacious dose of an immunogenic composition comprising PCV2 ORF2 protein,"

As discussed *supra* Claim 1.b, Blanchard discloses this element. Ex.1003 ¶227.

10.c. "wherein the symptoms are selected from the group consisting of PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate, decreased average daily weight gain, PCV2 viremia, and any combination thereof."

As discussed *supra* Claims 1 and 5, Blanchard discloses, both explicitly and inherently, a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection and PMWS (the disease associated with PCV2 infection), including PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate, decreased average daily weight gain, PCV2 viremia, and any combination thereof. Ex.1003 ¶228.

10. Claim 11

"The method of claim 10, wherein said PCV2 ORF2 protein comprises a protein selected from the group consisting of:

a. a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11;

b. any polypeptide that is at least 90% homologous to the polypeptide of a);

c. a polypeptide that is encoded by a polynucleotide comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 4; or

d. any polypeptide that is encoded by a polynucleotide that is at least 90% homologous to the polynucleotide of c)."

As discussed *supra* Claim 2, Blanchard discloses the elements of this claim. Ex.1003 ¶229.

11. Claim 12

"The method of claim 10, wherein said PCV2 ORF2 protein is a recombinant baculovirus-expressed ORF2 protein."

As discussed *supra* Claim 3, Blanchard discloses this element. Ex.1003 ¶230.

12. Claim 14

"The method of claim 10, wherein said immunogenic composition further comprises at least one additional component selected from the group consisting of a veterinary-acceptable carrier, a pharmaceutical-acceptable carrier, an adjuvant, cell culture supernatant, a preservative, a stabilizing agent, a viral vector, and an immunomodulatory agent."

As discussed *supra* Claim 1.c, Blanchard discloses this element. Ex.1003 ¶231.

13. Claim 15

"The method of claim 10, wherein the symptom is PCV2 virus shedding."

As discussed *supra* Claim 5, Blanchard discloses this element. Ex.1003 ¶232.

14. Claim 16

"The method of claim 10, wherein the symptom is lymphoid infection caused by PCV2."

As discussed *supra* Claim 6, Blanchard discloses this element. Ex.1003 ¶233.

15. Claim 17

"The method of claim 10, wherein the symptom is increased mortality rate in a group of piglets."

As discussed *supra* Claim 7, Blanchard discloses this element. Ex.1003 ¶234.

16. Claim 18

"The method of claim 10 wherein the symptom is decreased average daily weight gain."

As discussed *supra* Claim 8, Blanchard discloses this element. Ex.1003 ¶235.

17. Claim 19

"The method of claim 10, wherein the symptom is PCV2 viremia."

As discussed *supra* Claim 9, Blanchard discloses this element. Ex.1003 ¶236.

18. Claim 20

20.a. "A method for providing a protective effect against one or more symptoms of porcine circovirus type 2 (PCV2) infection comprising"

Blanchard discloses a method for providing a protective effect against one or more symptoms of porcine circovirus type 2 (PCV2) infection. As discussed *supra* Claim 1, in Trials 1 and 2, the piglets were administered a single dose of an ORF2 subunit vaccine that enhanced/elicited an immune response that protected the piglets from PCV2-associated symptoms after subsequent PCV2 challenge. Ex.1003 ¶237.

20.b. "administering to a piglet or group of piglets 2 to 6 weeks of age a single efficacious dose of an immunogenic composition comprising PCV2 ORF2 protein."

As discussed *supra* Claim 1.b, Blanchard discloses this element. Ex.1003 ¶238.

19. Claim 21

"The method of claim 20, wherein the one or more symptoms are selected from the group consisting of PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate in a group of piglets, decreased average daily weight gain, PCV2 viremia, and any combination thereof in piglets."

As discussed *supra* Claims 1, 5 and 10, Blanchard discloses this element. Ex.1003 ¶239.

20. Claim 22

"The method of claim 20, wherein said PCV2 ORF2 protein comprises a protein selected from the group consisting of:

a. a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11;

b. any polypeptide that is at least 90% homologous to the polypeptide of a);

c. a polypeptide that is encoded by a polynucleotide comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 4; or

d. any polypeptide that is encoded by a polynucleotide that is at least 90% homologous to the polynucleotide of c)."

As discussed *supra* Claim 2, Blanchard discloses the elements of this claim. Ex.1003 ¶240.

21. Claim 23

"The method of claim 20, wherein said PCV2 ORF2 protein is a recombinant baculovirus-expressed ORF2 protein."

As discussed *supra* Claim 3, Blanchard discloses this element. Ex.1003 ¶241.

22. Claim 25

"The method of claim 20, wherein said immunogenic composition further comprises at least one additional component selected from the group consisting of a veterinary-acceptable carrier, a pharmaceutical-acceptable carrier, an adjuvant, cell culture supernatant, a preservative, a stabilizing agent, a viral vector, and an immunomodulatory agent."

As discussed *supra* Claim 1.c, Blanchard discloses this element. Ex.1003 ¶242.

23. Claim 26

"The method of claim 21, wherein the symptom is PCV2 virus shedding."

As discussed *supra* Claim 5, Blanchard discloses this element. Ex.1003 ¶243.

24. Claim 27

"The method of claim 21, wherein the symptom is lymphoid infection caused by PCV2."

As discussed *supra* Claim 6, Blanchard discloses this element. Ex.1003 ¶244.

25. Claim 28

"The method of claim 21, wherein the symptom is increased mortality rate in a group of piglets."

As discussed *supra* Claim 7, Blanchard discloses this element. Ex.1003 ¶245.

26. Claim 29

"The method of claim 21, wherein the symptom is decreased average daily weight gain."

As discussed *supra* Claim 8, Blanchard discloses this element. Ex.1003 ¶246.

27. Claim 30

"The method of claim 21, wherein the symptom is PCV2 viremia."

As discussed *supra* Claim 9, Blanchard discloses this element. Ex.1003 ¶247.

C. GROUND 2: CLAIMS 1-3, 5-12, 14-23, AND 25-30 ARE ANTICIPATED BY JESTIN

Like Blanchard, Jestin teaches vaccine compositions comprising recombinant PCV2 ORF2 protein to protect against PCV2 infection (referred to therein as "PCV Type B" or "PCVB") infection. Ex.1003 ¶102. Jestin teaches that these vaccines "**will be administered one time** or several times, spread out over time." Ex.1005 at 27:45-46; Ex.1003 ¶102. Examples 5 and 8 of Jestin both teach that the administration of a single dose of PCV2 ORF2 protein prevented clinical symptoms associated with PCV2 infection. Ex.1003 ¶¶104-105.

1. Claim 1

Claim 1.a.

Jestin discloses a method of preventing and/or reducing one or more symptoms of PCV2 infection. First, Jestin teaches that its "invention is . . . directed at a pharmaceutical composition according to the invention for the prevention or treatment of an infection by [PCV2]." Ex.1005 at 25:33-35; *see also id.* at Abstract ("Pharmaceutical, including vaccines, compositions for preventing and/or treating viral infections caused by [PCV] and the use of vectors for preventing and/or treating diseases are provided."); *id.* at 11:25-34, Cl. 5, Ex.1009 at 11; Ex.1003 ¶249. Example 5 of Jestin discloses a prime-boost vaccination protocol comprising a single dose of PCV2 ORF2 protein that elicited an immune response conferring protection to prevent and/or reduce PCV2 symptoms after subsequent challenge. Ex.1003 ¶¶104, 250. Example 8 similarly discloses a vaccination protocol in which a single dose of ORF2 protein was administered that likewise conferred protection to prevent and/or reduce PCV2 symptoms after subsequent challenge. Ex.1003 ¶¶105, 250.

Claim 1.b.

Jestin discloses immunogenic compositions containing an efficacious dose of PCV2 ORF2 protein. *See, e.g.*, Ex.1005 at 11:25-34 (explaining that the

polypeptides according to the invention, including ORF2 polypeptides, are used as an "**immunogenic agent** to confer protection in pigs against infection by PWD [piglet weight loss disease] circovirus, especially of type B [i.e., PCV2]."); *id.* Cl. 5; Ex.1009 at 11; Ex.2003 ¶251.

Indeed, Patent-Owner has represented to the Board that "Jestin discloses the use of an **ORF2 protein** in its vaccine," and that this protein is "a recombinant protein." Ex.1009 at 15; Ex.1003 ¶252. Specifically, Jestin teaches a vaccine comprising the protein encoded by DNA SEQ ID No. 25. Ex.1005 at 3:52-67; Ex.1003 ¶252. SEQ ID No. 25 codes for the amino acid sequence in SEQ ID No. 26, which is the sequence for the ORF2 protein. Ex.1005 at 38:22-24; Ex.1009 at 15; Ex.1003 ¶¶253-255.

Jestin also discloses the use of this ORF2 protein in an efficacious dose. Specifically, Jestin explains that these compositions "contain an **effective quantity**" of ORF2 protein sufficient, for example, for "the modulation of the cellular replication of PWD [piglet weight loss disease] circovirus." Ex.1005 at 25:63-26:1; Ex.1003 ¶256.

In Example 5, *e.g.*, 5-week-old piglets received a single dose of a vaccine composition comprising insect cells transformed by BAC ORF2+ recombinant

baculoviruses. Ex.1003 ¶257. These cells express the PCV2 ORF2 protein and therefore this composition contains that protein. Ex. 1005 at 39:31-35; Ex.1003 ¶257. After PCV2 challenge, the vaccinated piglets "did not exhibit hyperthermia," "did not experience a decline in their growth, the the dmgs [daily mean gains] being comparable to those of uninfected animals," and "did not exhibit any particular clinical sign." Ex.1005 at 40:29-38; Ex.1003 ¶258. Jestin explains that the "results [of Example 5] in particular show that the proteins encoded by . . . ORF2 of [PCV2] according to the invention are immunogenic proteins inducing an efficacious protective response for the prevention of infection by [PCV2]." Ex.1005 at 40:47-51; Ex.1003 ¶259. Thus, this single dose of PCV2 ORF2 protein, together with injections of other compositions that did not contain PCV2 ORF2 protein, provided a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection. Ex.1003 ¶259.

Similarly, in Example 8, the piglets received a single dose of "ORF2 recombinant protein" in addition to receiving injections of the DNA vaccine. Ex. 1005 at 47:15-19; Ex.1003 ¶250. Jestin observed a higher "level of protection" for pigs "vaccinated with ORF2 protein." Ex.1005 at 47:18-22; 51-55. Ex.1003 ¶250.

Moreover, Jestin discloses vaccines with a dose of PCV2 ORF2 protein within the preferred dosage ranges provided in the '345 Patent. Ex.1003 ¶260. Indeed, Patent-Owner has taken the position that (i) Jestin discloses that its vaccine can comprise up to 10 micrograms ORF2 protein per kilogram weight of the animal, and (ii) based on "a study of piglet weight at 19.4, 38.4 and 62.4 days of life . . . the resulting Jestin vaccines would contain at least 63.3 µg, 133.0 µg, and 271.4 µg of antigen" per dose. Ex.1010 at 14; Ex.1003 ¶260. Thus, according to Patent-Owner's own calculation, the 5-week-old piglets in Jestin's Example 5 received a dose of approximately 133.0 µg of ORF2 protein, which is well within both the '345 Patent's preferable dose range of "0.2 to 400 µg/dose," as well as the narrower "more preferabl[e]" range of "0.3 to 300 µg/dose." Ex.1001 at 10:36-37; Ex.1003 ¶260.

Claim 1.c.

Jestin's vaccine also contains additional components selected from the claimed group, including both an "adjuvant" and/or a "pharmaceutical-acceptable carrier." For instance, the Jestin's ORF2 protein vaccine administered in Example 5 contains the adjuvant "AIF SEPPIC." Ex. 1001 at 38:65-67 ("This third injection comprises . . . 1 ml of AIF SEPPIC adjuvant."). Ex.1003 ¶261.

And more generally, Jestin teaches that its "vaccine combinations will **preferably** be combined with a **pharmaceutically acceptable vehicle** and, if need be, with **one or more adjuvants** of the appropriate immunity." Ex.1005 at 26:8-11; *see also id.* 3:44-51; 27:19-25 (listing several examples of "**adjuvants** of the appropriate immunity which are known to the person skilled in the art"). Ex.1003 ¶¶317-320. Indeed, Patent-Owner admits that "Jestin discloses that the vaccine may be combined with **one or more adjuvants**." Ex.1009 at 18; Ex.1003 ¶262.

2. Claim 2

As discussed *supra* Claim 1.b, Jestin teaches an immunogenic composition comprising the polypeptide in SEQ ID No. 26, *i.e.*, the PCV2 ORF2 protein. Ex.1005 at 3:52-67, 11:8-38:22-24; Ex.1003 ¶263. As shown by a comparison using the BLAST® sequence comparison algorithm, the polypeptide of SEQ ID No. 26 of Jestin is 93% identical to the polypeptide of SEQ ID No. 5 of the '345 Patent, which is at least 90% homologous as set forth in element 2.b. Ex.1003 ¶¶263-268.

3. Claim 3

As discussed *supra* Claim 1.b, Jestin discloses a vaccine composition comprising insect cells transformed by BAC ORF2+ recombinant baculoviruses to

express PCV2 ORF2 protein. Ex.1003 ¶269. The ORF2 protein expressed by those cells is a recombinant baculovirus-expressed ORF2 protein. Ex.1003 ¶¶269-273.

4. Claim 5

As discussed *supra* Claim 1, Jestin discloses, both expressly and inherently, a method for preventing PCV2 infection and a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection, including virus shedding. Ex.1003 ¶¶274-276.

5. Claim 6

As discussed *supra* Claim 1, Jestin discloses, both expressly and inherently, a method for preventing PCV2 infection and a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection, including lymphoid infection caused by PCV2. Ex.1003 ¶277.

6. Claim 7

As discussed *supra* Claim 1, Jestin discloses, both expressly and inherently, a method for preventing PCV2 infection and a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection, including increased mortality rate. Ex.1003 ¶278.

7. Claim 8

As discussed *supra* Claim 1, Jestin discloses, both expressly and inherently, a method for preventing PCV2 infection and a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection, including decreased average daily weight gain. Ex.1003 ¶¶279-280. Furthermore, as discussed *supra* Claim 1, Jestin explicitly discloses that the ORF2 protein vaccine in Example 5 prevented decreased average daily weight gain. Ex.1003 ¶280.

8. Claim 9

As discussed *supra* Claim 1, Jestin discloses, both expressly and inherently, a method for preventing PCV2 infection and a method for providing a protective effect to prevent and/or reduce clinical symptoms associated with PCV2 infection, including PCV2 viremia. Ex.1003 ¶281.

9. Claim 10

Claim 10.a.

As discussed *supra* Claim 1, Jestin discloses a method of aiding in the prevention and/or reduction of one or more symptoms of PCV2 infection. For example, the vaccination protocol in Example 5 comprises the administration of a

single dose of PCV2 ORF2 protein that aided in the prevention and/or reduction of one or more symptoms caused by PCV2 infection. Ex.1003 ¶282.

Claim 10.b.

As discussed *supra* Claim 1.b, Jestin discloses this element. Ex.1003 ¶283.

Claim 10.c.

As discussed *supra* Claims 1 and 5-9, the vaccine protocol in Jestin's ORF2 protein vaccine conferred protection against symptoms of PCV2 infection, including PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate, decreased average daily weight gain, PCV2 viremia, and any combination thereof. Ex.1003 ¶284.

10. Claim 11

As discussed *supra* Claim 2, Jestin teaches vaccine compositions comprising a PCV2 ORF2 protein that is at least 90% homologous to SEQ ID NO: 5 and therefore anticipates element 2.b. Ex.1003 ¶285.

11. Claim 12

As discussed *supra* Claims 1.b and 3, Jestin discloses this element. Ex.1003 ¶286.

12. Claim 14

As discussed *supra* Claim 1.c, Jestin discloses this element. Ex.1003 ¶287.

13. Claim 15

As discussed *supra* Claim 5, Jestin discloses this element. Ex.1003 ¶288.

14. Claim 16

As discussed *supra* Claim 6, Jestin discloses this element. Ex.1003 ¶289.

15. Claim 17

As discussed *supra* Claim 7, Jestin discloses this element. Ex.1003 ¶290.

16. Claim 18

As discussed *supra* Claim 8, Jestin discloses this element. Ex.1003 ¶291.

17. Claim 19

As discussed *supra* Claim 9, Jestin discloses this element. Ex.1003 ¶292.

18. Claim 20

Claim 20.a.

As discussed supra Claims 1.a and 10.a, Jestin discloses this element. Ex.1003 ¶293.

Claim 20.b.

As discussed supra Claim 1.b, Jestin discloses this element. Ex.1003 ¶294.

19. Claim 21

As discussed *supra* Claims 1 and 5-9, Jestin discloses this element. Ex.1003 ¶295.

20. Claim 22

As discussed *supra* Claim 2, Jestin discloses this element. Ex.1003 ¶296.

21. Claim 23

As discussed *supra* Claim 3, Jestin discloses this element. Ex.1003 ¶297.

22. Claim 25

As discussed *supra* Claim 1.c, Jestin discloses this element. Ex.1003 ¶298.

23. Claim 26

As discussed *supra* Claim 5, Jestin discloses this element. Ex.1003 ¶299.

24. Claim 27

As discussed *supra* Claim 6, Jestin discloses this element. Ex.1003 ¶300.

25. Claim 28

As discussed *supra* Claim 7, Jestin discloses this element. Ex.1003 ¶301.

26. Claim 29

As discussed *supra* Claim 8, Jestin discloses this element. Ex.1003 ¶302.

27. Claim 30

As discussed *supra* Claim 9, Jestin discloses this element. Ex.1003 ¶303.

D. GROUND 3: CLAIMS 1-3, 5-12, 14-23, AND 25-30 ARE OBVIOUS UNDER §103(A) OVER BLANCHARD IN VIEW OF THE KNOWLEDGE OF A POSA, AND ALSO IN VIEW OF JESTIN, MENG AND/OR FENAUX

As shown *supra* Grounds 1 and 2, Blanchard and Jestin anticipate Claims 1-3, 5-12, 14-23, and 25-30, respectively. Ex.1003 ¶304. To the extent Patent-Owner argues that those claims are limited to the administration of only a single injection of an ORF2 protein composition (and exclude the administration of other non-ORF2 protein compositions) and that therefore the claims are not anticipated because, in Patent-Owner's view, Blanchard and Jestin do not sufficiently demonstrate that symptoms are prevented, reduced, or protected against from just a single injection of ORF2 protein, then the claims are nevertheless obvious over Blanchard, in further view of Jestin, Meng, and Fenaux. *Id.* As explained below, a POSA reading those references would be motivated to adopt Meng and Fenaux's teaching of single-dose protocols for inoculating against PCV2 and would reasonably expect that a protective effect against symptoms could be achieved from a single dose of an ORF2 protein composition. *Id.*

Meng describes the immunogenicity of the recombinant PCV2 ORF2 protein, and teaches the use of a chimeric virus, PCV1-2, containing that protein as a single-dose vaccine. Ex.1003 ¶305. Fenaux demonstrates that a single dose of the live

PCV1-2 virus provides a protective effect against clinical symptoms associated with PCV2 infection. Ex.1003 ¶305. Thus, both Meng and Fenaux expressly teach the administration of a single efficacious dose of a composition comprising PCV2 ORF2 protein.

1. Motivation to Combine

A POSA would have been motivated to combine the teachings of Blanchard, Jestin, Meng, and Fenaux. Ex.1003 ¶306. First, all of these references teach immunogenic compositions containing PCV2 ORF2 protein to protect against PCV2 infection. Ex.1003 ¶306. Meng and Fenaux teach single-dose vaccine protocols involving immunogenic compositions that, like those taught in Blanchard and Jestin, comprise recombinant PCV2 ORF2 protein. Ex.1003 ¶307. And like the protein-containing compositions in Blanchard and Jestin, those vaccines are effective in preventing or reducing the symptoms associated with PCV2 infection. Ex. 1003 ¶308.

A POSA would be motivated to combine Meng's and Fenaux's teaching of administering the PCV1-2 virus in a single-dose regimen with Blanchard's and Jestin's PCV2 ORF2 subunit vaccines. Ex.1003 ¶309. For example, Meng explains that "[t]he **subunit vaccine** provides an advantage over other vaccines based on the

live virus since the subunit, such as the highly purified subunits of the virus, is less toxic than the whole virus." Ex.1007 at 20:3-5; *see also* Ex.1006 at 4572 ("[T]here is a current tendency towards the development of **non-replicating vaccines**, such as **subunit vaccines**. . . ."); Ex.1003 ¶¶310-311.

Moreover, it was well known in December 2005 that the recombinant ORF2 proteins of Jestin and Blanchard's vaccines form a virus-like particle ("VLP"), which is structurally similar to a live PCV2 virus but lacks the PCV2 genome, thus providing a safer and more commercially viable option than a live virus vaccine. Ex.1003 ¶¶312-314. Thus, a POSA would be motivated to administer an ORF2 protein-VLP vaccine as taught in Blanchard and Jestin. Ex.1003 ¶315.

A POSA would be highly motivated to administer the vaccine in a single dose. Ex.1003 ¶¶316-317. Single-dose vaccines reduce stress on piglets, decrease economic costs of vaccination, reduce trim loss at the packing plant, and result in a safer meat product for consumers. Ex.1003 ¶318. Indeed, Patent-Owner's declarant explained:

> Reducing the number of vaccine administrations for animals has been and still is highly desirable because each such administration subjects the animals to stress that is detrimental to their health, injection site reaction risks, injection site injury from the actual injection and from hazards such as broken needles, abscesses, general injury risk to the animals from the acts of administering

> vaccines and from the animals' reactions to such attempts, and, ultimately, their value at market. Furthermore, each administration of vaccine is costly in terms of expense of the dose of vaccine, time and labor for the individuals gathering the animals and administering the vaccine, and increases the risk of injury to those administering the vaccines.

Ex.1055 ¶13; Ex.1003 ¶¶319-320.

Thus, a POSA would have been motivated to combine Meng's and Fenaux's single-dose regimen with Blanchard's recombinant ORF2 protein-VLP vaccine because: (1) all four references are directed to substantially the same subject matter; (2) single dose regimens were well known and preferred in the prior art; (3) Fenaux demonstrated that a single dose of PCV1-2 virus containing PCV2 ORF2 protein provides a substantial protective effect against clinical symptoms; and (4) the recombinant ORF2 protein VLPs in Blanchard's and Jestin's subunit vaccines are structurally similar to Meng's and Fenaux's PCV1-2 virus, but provide a safer and more commercially viable option. Ex.1003 ¶321.

*2. **Reasonable Expectation of Success***

A POSA would also have a reasonable expectation that a single dose of an ORF2 subunit vaccine would exhibit a protective effect against clinical symptoms associated with PCV2 infection in view of the prior art. Ex.1003 ¶322.

First, both Blanchard and Jestin teach ORF2 protein vaccines comprising recombinant PCV2 ORF2 protein in an amount that falls squarely within the preferred dosage ranges stated in the '345 Patent. *Supra* Section VII.B&C, Claim 1.a; Ex.1003 ¶¶323-324. Indeed, Trial 1 of Blanchard demonstrates the efficacy of a protocol in which just a single dose of a composition comprising an efficacious amount of ORF2 protein was administered. Ex.1003 ¶323.

Second, the data in Trial 2 of Blanchard demonstrate that within 14 days of a single dose of its ORF2 subunit vaccine the piglets seroconverted (*i.e.*, developed antibodies). *Supra* Section VII.B, Claim 1.b; Ex.1003 ¶¶325-336. The antibodies induced by Blanchard's ORF2 subunit vaccine were effective in neutralizing the PCV2 virus and preventing clinical symptoms after challenge, demonstrating that the first dose of Blanchard's ORF2 subunit vaccine was enough to produce neutralizing antibodies. Ex.1003 ¶¶323-336. Furthermore, while Trial 2 involved the later administration of a second dose, the data there shows that the level of antibodies was roughly the same before and after that second dose—again providing a reasonable expectation that a single dose of that PCV2 ORF2 protein-containing composition would be sufficient to prevent or reduce and provide a protective effect against clinical symptoms. Ex.1003 ¶¶323-336.

Third, Meng and Fenaux teach that a single dose of a composition containing PCV2 ORF2 protein is sufficient to protect against clinical symptoms associated with a PCV2 infection. For example, the data in Fenaux show that a single dose of its ORF2 protein-containing composition induced the production of antibodies to ORF2 protein in all 12 piglets studied and protected against clinical symptoms associated with PCV2 infection. Ex.1003 ¶337. Indeed, both Jestin and Meng expressly teach that the ORF2 protein can be administered either "one time or several times" (Ex.1005 at 27:45-46) and "in a single dose or in repeated doses" (Ex.1007 at 23:15) to vaccinate against PCV2. Ex.1003 ¶324.

In view of the above, a POSA would have had more than a reasonable expectation that a single-dose recombinant ORF2 subunit vaccines would prevent clinical symptoms associated with PCV2 infection because: (1) Blanchard and Jestin teach ORF2 subunit vaccines comprising an amount of recombinant PCV2 ORF2 protein within the preferred dosage range taught in the '345 Patent; (2) Blanchard shows that the first dose of that vaccine, by itself, was sufficient to induce the production of antibodies that neutralized the PCV2 virus; (3) the level of antibodies induced by that first dose remained relatively constant after a second injection and after challenge; (4) both the antibodies produced by Blanchard's ORF2 subunit

vaccine and the antibodies produced by administration of Meng's and Fenaux's PCV1-2 virus were specific to the same protein, ORF2 protein; (5) both Jestin and Meng expressly state that these vaccines can be administered in single dose protocols; and (6) Meng and Fenaux teach that a single dose of an immunogenic composition comprising the PCV1-2 virus, which is structurally similar to the recombinant ORF2 protein VLP in Blanchard's ORF2 subunit vaccine, provided a substantial protective effect against clinical symptoms associated with PCV2 infection. Ex.1003 ¶¶323-337. Moreover, as of December 2005 it was well known that inactivated and/or subunit vaccines could provide protective effects against signs of infection in pigs after a single dose. Ex.1003 ¶¶338-346. Furthermore, several inactivated vaccines were commercially available for single-dose administration at that time. Ex.1003 ¶347.

In sum, a POSA would have been motivated to combine Meng's and Fenaux's teaching of a single dose of PCV1-2 virus with Blanchard's and Jestin's PCV2 ORF2 subunit vaccine, and would have a reasonable expectation that a single dose of that vaccine would prevent clinical symptoms associated with PCV2 infection. Thus, to the extent they are not anticipated, Claims 1-3, 5-12, 14-23, and 25-30 are obvious

under §103(a) over Blanchard in view of the knowledge of a POSA, and also in view of Jestin, Meng and/or Fenaux.

E. GROUND 4: CLAIMS 4, 13, AND 24 ARE OBVIOUS UNDER §103(A) OVER BLANCHARD AND/OR JESTIN IN VIEW OF THE KNOWLEDGE OF A POSA, AND ALSO IN VIEW OF HALBUR AND THOMAS

To the extent Patent-Owner contends that the three-week limitation of claims 4, 13, and 24 is not taught by the references in Grounds 1-3, that limitation is taught by Halbur and Thomas. Ex.1003 ¶348. Thus, these claims are obvious in further view of the same. *Id.*

Both Halbur and Thomas teach the vaccination of piglets against PCV2 infection at three weeks of age. Ex.1003 ¶349. Like Meng and Fenaux, Halbur and Thomas describe the administration of an immunogenic composition comprising chimeric PCV1-2 virus. Ex.1003 ¶349. A POSA would have been motivated to combine that teaching from Halbur and Thomas with Blanchard and/or Jestin because the recombinant ORF2 VLP proteins in Blanchard and Jestin are structurally similar to the PCV2 ORF2 capsid protein of the PCV1-2 virus in Halbur and Thomas, and vaccination at three weeks of age is both common and advantageous, as explained below. Ex.1003 ¶349.

Claim 4: "The method of claim 1, wherein said administering of the single efficacious dose occurs in piglets 3 weeks of age."

Claim 13: "The method of claim 10, wherein said administering of the single efficacious dose occurs in piglets 3 weeks of age."

Claim 24: "The method of claim 20, wherein said administering of the single efficacious dose occurs in piglets 3 weeks of age."

Halbur discloses the administration of a single efficacious dose of "live chimeric [PCV2] vaccine at **3 weeks of age**." Ex.1011 at 18; Ex.1003 ¶350. Thomas is a publication describing the same study as in Halbur and likewise teaching administration of a single dose to three-week-old piglets. Ex.1069 at 23; Ex.1003 ¶351.

Both Halbur and Thomas concluded that a single dose of PCV1-2 live vaccine is effective at eliciting a protective immune response in piglets at three weeks of age. Ex.1011 at 18; Ex. 1069 at 24; Ex.1003 ¶¶352-353. Indeed, Halbur and Thomas observed respiratory scores to be significantly lower for the vaccinated groups compared to the non-vaccinated groups after PCV2 challenge. Ex.1011 at 18; Ex.1069 at 24; Ex.1003 ¶354. They also observed an anamnestic response in vaccinated groups with low maternity antibody levels; *i.e.*, the single dose of the PCV1-2 live vaccine was able to generate immunological memory such that there

was a rapid, boosting response to PCV2 challenge. Ex.1011 at 18; Ex.1069 at 24; Ex.1003 ¶¶50, 355-357.

In addition, a POSA would be motivated to vaccinate at three weeks of age based on her general understanding of PCV2 infection and PMWS. Ex.1003 ¶358. "PMWS primarily affects pigs between 5-18 weeks of age," Ex.1007 at 4:11, and it was known in December 2005 that there was a particularly high fatality rate for piglets infected at 5-12 weeks of age. Ex.1012 at 2494; Ex.1003 ¶359. Because it typically takes some time to develop antibodies following vaccination, a POSA would be motivated to vaccinate even earlier to allow time for the animal to build resistance. Ex.1003 ¶358. Also, at the age of three weeks, piglets begin to lose their maternally derived antibodies (MDAs), which provide some natural protection against PCV2 infection. Ex.1003 ¶359. Accordingly, there is a limited window of time in which piglets must be vaccinated to prevent PMWS. Ex.1003 ¶360; *see also* Ex.1012 at 10:37-42 ("Preferably, piglets are first inoculated within the first week of life or within the third week of life (e.g., at the time of weaning)."). Indeed, Blanchard itself teaches the vaccination of piglets at close to three weeks of age (25 days). Ex.1006 at 4566; Ex.1003 ¶361.

Thus, a POSA would have been motivated to administer a single dose of Blanchard's and/or Jestin's recombinant ORF2 protein vaccine to piglets three weeks of age as taught by Halbur and Thomas, and as known by a POSA. Ex.1003 ¶362. And in view of the knowledge of a POSA and the results in Halbur and Thomas, a POSA would have reasonably expected that a single-dose injection of the recombinant ORF2 vaccine administered to piglets at that age would provide a protective effect against symptoms of PCV2 infection. Ex.1003 ¶362.

F. GROUND 5: CLAIMS 1-2, 4-11, 13-22, AND 24-30 ARE ANTICIPATED UNDER §102(B) OVER HALBUR

As discussed *supra* Ground 4, Halbur describes the vaccination of pigs with a single dose of a live chimeric PCV1-2 vaccine at three weeks of age. The vaccinated pigs were challenged with wild-type PCV2 at nine weeks of age to determine the vaccine's efficacy. Ex.1003 ¶363.

1. Claim 1

Claim 1.a.

Halbur teaches a method of preventing and/or reducing one or more symptoms of PCV2 infection. Ex.1011 at 17-18; Ex.1003 ¶364. It describes a study in which a single dose of PCV2 ORF2 protein in the form of a live chimeric PCV1-2 vaccine

elicited an immune response that conferred protection to prevent and/or reduce PCV2 symptoms after PCV2 challenge. Ex.1011 at 18; Ex.1003 ¶365.

Claim 1.b.

As discussed *supra* Ground 4, Halbur's live chimeric PCV1-2 vaccine is an immunogenic composition comprising PCV2 ORF2 protein as its capsid protein. Ex.1011 at 17-18; Ex.1003 ¶366.

Halbur teaches the administration of a single efficacious dose of that ORF2 protein. Ex.1011 at 18; Ex.1003 ¶367. Specifically, a single injection of the live PCV1-2 vaccine was administered to piglets three weeks of age. Ex.1011 at 18; Ex.1003 ¶367. The vaccinated piglets were then challenged with wild-type PCV2 at nine weeks of age, and their average daily weight gain, elevated temperature, respiratory scores, and PCV2 antibody levels were monitored. Ex.1011 at 18; Ex.1003 ¶368. Gross and microscopic lesions were scored after the pigs were necropsied at 63 days post-vaccination. Ex.1011 at 18; Ex.1003 ¶368.

Halbur discloses that respiratory scores were significantly higher (meaning that those pigs exhibited more severe clinical symptoms) for non-vaccinated groups compared to Groups 1-3. Ex.1011 at 18; Ex.1003 ¶369. Halbur observed that Groups 1 and 2 had a rapid, boosting response by 14 days after PCV2

challenge. Ex.1011 at 18; Ex.1003 ¶373. Halbur also noted that the control Group 7 had significantly more severe lymphoid depletion than Groups 1 and 2. Ex.1011 at 18; Ex.1003 ¶370. Thus, Halbur concludes that "immune protection was induced by the chimeric PCV2 vaccine," at least for those piglets with passive antibody levels <0.5 at the time of vaccination. Ex.1011 at 18; Ex.1003 ¶371.

Thus, Halbur teaches that a single dose of a composition comprising PCV2 ORF2 protein administered to piglets at three weeks of age was effective to elicit an immune response to prevent and/or reduce clinical symptoms associated with PCV2 infection. Ex.1003 ¶372. While that finding applied to piglets with relatively low levels of passive MDAs the claims of the '345 Patent are not limited to vaccinating piglets with high levels of MDAs. Ex.1003 ¶372. Thus, Halbur teaches this element.

Claim 1.c.

Halbur's PCV1-2 vaccine also comprises additional components from the claimed group, including a viral vector and a veterinary-acceptable carrier. Ex.1003 ¶373. First, the PCV1-2 virus in Halbur's vaccine is a viral vector. Ex.1003 ¶374. Second, while the particular carrier is not expressly disclosed, a POSA would understand that the PCV1-2 virus in Halbur was necessarily

administered in some sort of veterinary-acceptable carrier because it was injected intramuscularly and therefore would have to be in solution. Ex.1003 ¶374. The '345 Patent broadly describes a veterinary-acceptable carrier as "any and all solvents" (*e.g.*, water). Ex.1001, 11:46-47; Ex.1003 ¶374. Thus, Halbur discloses this element. Ex.1003 ¶375.

2. Claim 2

Halbur's PCV1-2 virus is the same PCV1-2 virus disclosed in Fenaux and Meng. Ex.1011 at 17-18; Ex.1003 ¶¶376-377. The ORF2 protein expressed by and contained in that PCV1-2 virus is encoded by the DNA sequence in Figure 10 of Meng. Ex.1003 ¶377; Ex.1007 at 13:20-21 ("Figure 10 represents the DNA sequence of the immunogenic **ORF2 capsid gene of cloned the chimeric PCV1-2 DNA** (which corresponds to SEQ ID NO: 3)"). According to BLAST®, the DNA sequence of Figure 10 of Meng is 99% identical to the ORF2 region of SEQ ID No. 3 of the '345 Patent, which is at least 90% homologous as set forth in element 2.d. Ex.1003 ¶¶375, 378-381.

3. Claim 4

As discussed *supra* Claim 1.b, Halbur administered a single efficacious dose in piglets at three weeks of age. Ex.1003 ¶382.

4. Claim 5

The ’345 Patent states that the symptoms of PCV2 infection include PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate, decreased average daily weight gain, and PCV2 viremia. Ex.1001 at Cls. 5-8; Ex.1003 ¶383. A vaccine that provides a protective effect against PCV2 challenge will prevent, reduce, and/or protect against these symptoms. Ex.1003 ¶383. As discussed *supra* Claim 1.b, Halbur’s PCV1-2 vaccine elicits an immune response that provides a protective effect to prevent and/or reduce symptoms associated with PCV2 infection. Ex.1003 ¶384. For example, after PCV2 challenge, Halbur observed respiratory scores, which are also symptoms associated with PCV2 infection, to be significantly lower for vaccinated groups compared to non-vaccinated groups. Ex.1011 at 18; Ex.1003 ¶385. Halbur also observed an anamnestic response in vaccinated pigs with low maternity antibody levels. Ex.1011 at 18; Ex.1003 ¶385. Thus, Halbur explicitly and inherently discloses that a single dose of the live PCV1-2 vaccine confers protective immunity to prevent and/or reduce symptoms of PCV2 infection, including virus shedding. Ex.1003 ¶386.

5. Claim 6

As discussed *supra* Claims 1 and 5, Halbur's vaccine conferred protection to prevent and/or reduce symptoms of PCV2 infection, including lymphoid infection. Ex.1003 ¶387.

6. Claim 7

As discussed *supra* Claims 1 and 5, Halbur's vaccine conferred a protective effect to prevent and/or reduce symptoms of PCV2 infection, including increased mortality rate. Ex.1003 ¶388.

7. Claim 8

As discussed *supra* Claims 1 and 5, Halbur's vaccine conferred a protective effect to prevent and/or reduce symptoms of PCV2 infection, including decreased average daily weight gain. Ex.1003 ¶389.

8. Claim 9

As discussed *supra* Claims 1 and 5, Halbur's vaccine conferred a protective effect to prevent and/or reduce symptoms of PCV2 infection, including PCV2 viremia. Ex.1003 ¶390.

9. Claim 10

Claim 10.a.

Halbur discloses a method of aiding in the prevention and/or reduction of one or more symptoms of PCV2 infection. In Halbur, a single dose of the PCV1-2 virus containing the ORF2 capsid protein elicited an immune response that aided in the prevention and/or reduction of one or more symptoms caused by PCV2 infection for those piglets having relatively low levels of maternal antibodies. Ex.1003 ¶391.

Claim 10.b.

As discussed *supra* Claim 1.b, Halbur discloses this element. Ex.1003 ¶392.

Claim 10.c.

As discussed *supra* Claims 1 and 5-9, Halbur's vaccine conferred protection against symptoms of PCV2 infection, including PCV2 virus shedding, lymphoid infection caused by PCV2, increased mortality rate, decreased average daily weight gain, PCV2 viremia, and any combination thereof. Ex.1003 ¶393.

10. Claim 11

As discussed *supra* Claim 2, Halbur discloses this element. Ex.1003 ¶394.

11. Claim 13

As discussed *supra* Claim 1.b, Halbur discloses this element. Ex.1003 ¶395.

12. Claim 14

As discussed *supra* Claim 1.c, Halbur discloses this element. Ex.1003 ¶396.

13. Claim 15

As discussed *supra* Claim 5, Halbur discloses this element. Ex.1003 ¶397.

14. Claim 16

As discussed *supra* Claim 6, Halbur discloses this element. Ex.1003 ¶398.

15. Claim 17

As discussed *supra* Claim 7, Halbur discloses this element. Ex.1003 ¶399.

16. Claim 18

As discussed *supra* Claim 8, Halbur discloses this element. Ex.1003 ¶400.

17. Claim 19

As discussed *supra* Claim 9, Halbur discloses this element. Ex.1003 ¶401.

18. Claim 20

Claim 20.a.

As discussed *supra* Claims 1.a and 10.a, Halbur discloses this element. Ex.1003 ¶402.

Claim 20.b.

As discussed *supra* Claim 1.b, Halbur discloses this element. Ex.1003 ¶403.

19. Claim 21

As discussed *supra* Claims 1 and 5-9, Halbur discloses this element. Ex.1003 ¶404.

20. Claim 22

As discussed *supra* Claim 2, Halbur discloses this element. Ex.1003 ¶405.

21. Claim 24

As discussed *supra* Claim 1.b, Halbur discloses the administration of a single efficacious dose to piglets at three weeks of age. Ex.1003 ¶406.

22. Claim 25

As discussed *supra* Claim 1.c, Halbur discloses this element. Ex.1003 ¶407.

23. Claim 26

As discussed *supra* Claim 5, Halbur discloses this element. Ex.1003 ¶408.

24. Claim 27

As discussed *supra* Claim 6, Halbur discloses this element. Ex.1003 ¶409.

25. Claim 28

As discussed *supra* Claim 7, Halbur discloses this element. Ex.1003 ¶410.

26. Claim 29

As discussed *supra* Claim 8, Halbur discloses this element. Ex.1003 ¶411.

27. Claim 30

As discussed *supra* Claim 9, Halbur discloses this element. Ex.1003 ¶412.

G. GROUND 6: CLAIMS 1-2, 4-11, 13-22, AND 24-30 ARE OBVIOUS UNDER §103(A) OVER HALBUR IN VIEW OF THE KNOWLEDGE OF A POSA, AND ALSO IN VIEW OF FENAUX AND THOMAS

As discussed *supra* Ground 5, Halbur discloses all of the limitations of Claims 1-2, 4-11, 13-22, and 24-30. To the extent Patent-Owner argues that Halbur does not teach an additional component in its immunogenic composition (*e.g.*, Claim 1.c), the three-week limitation (*e.g.*, Claim 3), and/or protective effects against symptoms associated with PCV2 infection (*e.g.*, Claims 5-9), those limitations are obvious to a POSA in view of Fenaux and Thomas. Ex.1003 ¶413.

As discussed *supra* Grounds 4 and 5, Fenaux teaches the administration of an immunogenic composition comprising the chimeric PCV1-2 virus comprising PCV2 ORF2 protein. Ex.1003 ¶414. That composition was stored in minimum essential medium (MEM) and antibiotics. Ex.1008 at 6298, citing to Ex. 1071; Ex.1003 ¶414. Thus, the PCV1-2 vaccine described in Halbur, Fenaux, and Thomas comprises both MEM, a "veterinary-acceptable carrier" and/or "pharmaceutical-acceptable carrier," and antibiotics, *i.e.*, "preservatives." Ex.1003 ¶415.

Moreover, in Fenaux, a single dose of the live PCV1-2 vaccine was administered to piglets (Group 3) at nine weeks of age. Ex.1008 at 6298; Ex.1003 ¶416. After PCV2 challenge, Group 3 pigs did not show any clinical signs of PCV2 infection for the duration of the study. Ex.1008 at 6300 ("Clinical signs characteristic of PMWS were not observed in any animals of groups 1, 2, 3, and 4 for the duration of the study."); Ex.1003 ¶417. They also did not have detectable PCV2 viremia and had reduced virus loads in the lymph nodes compared to pigs in the control group. Ex.1008 at 6301 ("no PCV2 viremia was detected in vaccinated pigs after challenge"); *id*. ("Vaccinated pigs also had reduced PCV2 genomic copy viral loads in the lymph nodes."); Ex.1003 ¶418. Fenaux concludes that "[t]hese data indicate that PCV1-2 candidate vaccine can prevent PCV2 viremia and significantly reduce the amount of PCV2 virus in the lymphoid tissues." Ex.1008 at 6301; Ex.1003 ¶419.

1. Motivation to Combine

A POSA would have been motivated to combine the teachings of Halbur, Fenaux, and Thomas because they were published by various members of the same research group and relate to the same PCV1-2 live vaccine. Ex.1003 ¶420. Fenaux concludes that "[s]ince many newborns in commercial swine farms have

PCV2 maternal antibodies following colostrum uptake, future studies with larger numbers of animals with different levels of maternal antibody are warranted to confirm our preliminary results." Ex.1003 ¶421.

As discussed *supra* Ground 4, Halbur and Thomas describe a follow-up study to the one in Fenaux to determine the efficacy of Fenaux's PCV1-2 vaccines in very young piglets (three weeks of age). Halbur and Thomas demonstrate that the ORF2 protein-containing vaccine was effective in three-week-old piglets. Ex.1003 ¶422. Thus, a POSA would have been motivated to combine Fenaux's teachings concerning the composition and efficacy of its PCV1-2 vaccine with that used in Halbur/Thomas's follow-up study. Ex.1003 ¶423.

2. Reasonable Expectation of Success

In light of the combined teachings of Halbur, Fenaux and Thomas, a POSA would have reasonably expected that the PCV1-2 vaccine may additionally comprise components like (i) MEM, *i.e.*, a "veterinary-acceptable carrier" and/or "pharmaceutical-acceptable carrier," and/or (ii) antibiotics as "preservatives." Ex.1003 ¶424.

As discussed above, Fenaux teaches that a single dose of an immunogenic composition comprising PCV2 ORF2 protein and these additional components

provides a protective effect against symptoms associated with PCV2 infection. Ex.1003 ¶425. Halbur/Thomas also show that a single dose of the same vaccine induces protective effects in piglets having low maternal antibody level at three weeks of age. Ex.1003 ¶425. Thus, a POSA would have reasonably expected that administering a single dose of the PCV1-2 vaccine composition to piglets at three weeks of age would elicit an immune response that confers protective effect against symptoms associated with PCV2 infection or against PCV2 infection. Ex.1003 ¶426.

VIII. CONCLUSION

For all of the reasons set forth above, there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the 30 claims challenged in this petition.

IX. CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for the Petitioner declares that the argument section of this Petition (Section I and Sections III-VIII) has a total of 13,986 words, according to the word count tool in Microsoft Word™.

DATED: November 30, 2018

Respectfully Submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), (b) on Patent-Owner via UPS overnight mail of a copy of this Petition for *Inter Partes* Review and supporting materials on Patent-Owner at the correspondence address of record for the '345 Patent:

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