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 IPR2018-01789
Patent No. 9,011,872

EXHIBIT 2112

UNITED STATES PATENT AND TRADEMARK OFFICE

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

v.

Boehringer Ingelheim Vetmedica, Inc.,
Patent-Owner.

Case No. Unassigned

U.S. Patent No. 9,011,872

Petition for *Inter Partes* Review of U.S. Patent No. 9,011,872

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I. INTRODUCTION

Intervet Inc. ("Petitioner") hereby petitions for inter partes review ("IPR"), asking the Board to cancel all claims of U.S. Patent No. 9,011,872 ("the '872 Patent," Ex.1001) because they are unpatentable under 35 U.S.C. §§ 102 and 103.

The '872 Patent claims immunogenic compositions comprising a particular protein (ORF2) from a particular porcine virus (PCV2) which is sufficient to provide a protective effect against clinical symptoms associated with PCV2 infection after a single dose, and methods of administering that composition. The prior art teaches these same compositions and methods, as well as the protective effect against clinical symptoms associated with PCV2 infection that they provide. To the extent Patent-Owner argues 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 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

is 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 ’872 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.

In addition to this petition, Petitioner is concurrently filing a second petition for IPR of the '872 Patent raising different and additional grounds for cancelling the claims of the '872 Patent.

Finally, Petitioner notes that the European counterpart of the '872 Patent, EP2281829, was revoked by the Opposition Division of the European Patent Office on September 12, 2018. EP2281829 claims use of the transitional phrase "consists of," which limits the use of the claimed vaccine in a one-dose regimen and excludes any additional administration of the same vaccine and/or other composition(s). For example, Claim 1 of EP2281829 recites:

> "1. A vaccine comprising 4 to 400 µg/dose recombinant PCV2 ORF2 protein for use in a method of preventing PCV2 infection in a pig, wherein **said method consists of the administration of one dose** of said vaccine to said pig."

Ex.1055 at Cl. 1[1]. The Opposition Division found that the patent specification did not provide support for such one-dose regimen and the closed language "consists of," and thus, EP2281829 was revoked. 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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[1] Emphases added throughout unless otherwise noted.

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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), $37,100 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 '872 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 1-24) of the '872 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 1-5, 11-16, and 18-24 are anticipated under §102(b) by Blanchard;
- GROUND 2: Claims 1-5, 11-13, 15-16 and 18-24 are anticipated under §102(b) by Jestin;
- GROUND 3: Claims 1-5, 11-16, and 18-24 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 6-10 are obvious under §103(a) over Blanchard and/or Jestin, in view of the knowledge of a POSA, and also in view of Bublot
- GROUND 5: Claim 17 is obvious under §103(a) over Blanchard and/or Jestin, in view of the knowledge of a POSA, and also in view of Halbur

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 '872 Patent issued from Application No. 13,728,228 (the "'228 Application"), filed December 27, 2012, which claims priority through a series of applications to Provisional Application No. 60,640,510, filed December 30, 2004. Ex.1001. Petitioner does not believe the '872 Patent claims are entitled to the benefit of the December 30, 2004 Provisional Application, but because the references in the grounds herein predate that application, the '872 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 2004 ("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 (hereafter, "POSA"). 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 ¶143.

B. SCOPE AND CONTENT OF THE ART BEFORE DECEMBER 2004

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 '872 Patent, an "immunogenic composition" is a "composition of matter that comprises at least one antigen which elicits an immunological response in the host of a cellular and/or antibody-mediated immune response to the composition or vaccine of interest." Ex.1001 at 5:18-22; Ex.1003 ¶35. In this context, the antigen resembles some aspect of the pathogen, e.g., a protein from the exterior of a virus that causes the disease the vaccine is intended to prevent. 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 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 cell 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 2004, 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 2004, 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. Clinical 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 2004, 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. The '872 Patent itself acknowledges that vaccines using ORF2 proteins were already known in the art. Ex.1001 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 2004, 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 contain or express a recombinant ORF2 protein as their antigenic component: subunit vaccines, DNA vector vaccines, and live and inactivated chimeric PCV1-2 virus vaccines.[2] Ex.1003 ¶¶85-92. Fenaux continued the work of Meng, focusing on a live chimeric PCV1-2 virus vaccine, which comprises recombinant ORF2 protein. Ex.1003 ¶¶93-99. As discussed in more detail below, Fenaux's PCV1-2 virus vaccine was demonstrated 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 provided such a protective effect. Ex.1003 ¶¶100-101.

Jestin and Blanchard describe subunit vaccines containing recombinant ORF2 protein as their antigenic component. Ex.1003 ¶¶102-117. As discussed in more detail below, Jestin discloses the administration of a single dose of a subunit vaccine containing an effective amount of the ORF2 protein according to the '872 Patent.

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

Blanchard discloses data showing that its ORF2 subunit vaccine provides a protective effect against symptoms of PCV2 infection after a single dose.

In addition, as of December 2004, other researchers, for example Parisot and Reynaud, were studying the efficacy of single-dose vaccines containing inactivated PCV2 virus, and thus recombinant 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 '872 PATENT

The '872 Patent is directed to "an immunogenic composition effective for inducing an immune response against PCV2, and methods for producing those immunogenic compositions." Ex.1001 at 1:44-47; Ex.1003 ¶118. It has four independent claims: composition claims 1, 20, and 21, and method claim 15. Ex.1003 ¶119. The composition claims are directed to an immunogenic composition comprising an effective amount of PCV2 ORF2 protein that provides a protective effect against clinical symptoms associated with a PCV2 infection after a single dose. Ex.1003 ¶120.

Claim 15 is directed to a method of protecting piglets against clinical symptoms associated with PCV2 infection after administering a single dose of the

claimed immunogenic composition "comprising the step of" administering that immunogenic composition. Ex.1003 ¶121.

As detailed below, Blanchard and Jestin each teach every element of the '872 Patent claims, and Meng and Fenaux further support the obviousness of the claims. To the extent any element is not explicitly discussed in these references, it is a routine aspect of vaccine formulation 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 ¶¶145-157. The primary references in the grounds herein are Blanchard and Jestin. The Examiner did not rely on Jestin[3] as the basis for any rejection. Blanchard was cited as a secondary reference in a non-final rejection, but the Examiner never referred to its substance, explained why it was cited in the rejection, nor otherwise discussed its teachings. Ex.1003 ¶148.

[3] A different Jestin patent (U.S. Patent No. 7,223,594) was the basis for rejections during the prosecution of related applications U.S. Application Nos. 13/190,452 and 12/137,909.

Blanchard was subsequently dropped without explanation from the obviousness combination the Examiner considered and not included in the final rejection that was overcome. Ex.1003 ¶¶152-154.

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 subunit vaccine comprises an effective amount of recombinant ORF2 protein according to the '872 Patent (Ex.1010), the expert testimony submitted by Petitioner here (Ex.1003), and secondary references Meng, Fenaux,[4] Bublot and Halbur.

Even for those references that are cited on the face of the '872 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

[4] A different Fenaux article (Fenaux 2000) served as a secondary reference for two rejections. Fenaux 2000 is directed to genetic testing and characterization of PCV1 and PCV2 viruses. Unlike the Fenaux reference in the grounds herein, Fenaux 2000 does not describe any testing of immunogenic compositions. Ex.1013.

reasonable expectation that a single dose of those vaccines 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-D. 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 "protective effect" and "single dose" language the applicant added during prosecution. The prior art in the grounds herein describes the same compositions claimed in the '872 Patent, i.e., vaccines comprising ORF2 protein within the dose ranges in the '872 Patent and an inactivated viral vector, and teaches how to make and administer them. 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. *Id.* The '872 Patent claims were allowed based on the

addition of this inherent property without any consideration of whether the prior art disclosed the same immunogenic compositions and methods.

Therefore, the grounds here are not the same, nor are they substantially the same, as the arguments considered during prosecution. Accordingly, any argument for non-institution under 35 U.S.C. § 325(d) is misplaced. In addition, Petitioner notes that concurrent with this petition, it is filing another petition seeking IPR of the '872 Patent based on different grounds and arguments. Because neither petition is a "follow-on" to the other, there is likewise no basis for the Board to decline institution under § 314(a).

E. CLAIM CONSTRUCTION

Presently in IPR, claims receive the broadest reasonable interpretation ("BRI") supported by the specification. 37 C.F.R. § 42.100(b). At least the following terms require construction:

1. "Comprising . . . Recombinant PCV2 ORF2 protein" and "Comprising the step of"

When construed under its BRI, the "comprising recombinant PCV2 ORF2 protein" element in independent claims 1, 20 and 21 may encompass any composition that contains any ORF2 protein that is a product of recombinant DNA

technology. This is a "comprising" term, so it does not exclude compositions that contain other components, such as DNA, other viral proteins, cellular lysate, or pharmaceutical excipients in addition to claimed components. Ex.1003 ¶¶122-126, 130.

Likewise, when construed under its BRI, the "comprising the step of" element of independent claim 15 does not exclude additional steps, including administration of other compositions. Ex.1003 ¶127,130.

2. "Effective Amount of Recombinant PCV2 ORF2 protein"

When construed under its BRI, the "effective amount" limitation in independent claims 1, 15, and 21 at least encompasses an amount of PCV2 ORF2 protein anywhere in the range from 0.2 to about 400 μg/dose, which is the broadest dosage range described in the '872 Patent specification as "effective for inducing the desired immune response, namely reducing the incidence of or lessening the severity of clinical signs resulting from PCV2 infection." Ex.1001 at 19:55-20:10; *see also id.* at Claim 11. Consistent with this range, the '872 Patent states that "recombinant baculovirus expressed PCV2 ORF2 protein is effective is [sic] in very low concentrations, which means concentrations up to 0.25 μg/dose." Ex.1001 at 22:52-56; Ex.1003 ¶¶128,130.

3. "Provides a Protective Effect Against Clinical Symptoms Associated with a PCV2 Infection"

When construed under its BRI, the "protective effect" element of independent claims 1, 15, 20, and 21 encompasses a protective effect of any magnitude, duration, or type, against any clinical symptom associated with a PCV2 infection or against PCV2 infection itself. There is no minimum level of protection specified in the specification or claims. Likewise, the claim is not limited to protection against a particular symptom or set of symptoms. Thus, any degree of protective effect against any clinical symptoms is sufficient.

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, 51 USPQ2d 1943, 1947 (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 Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *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 1-5, 11-16, AND 18-24 ARE ANTICIPATED UNDER § 102(B) BY BLANCHARD

Blanchard teaches a composition comprising recombinant PCV2 ORF2 protein (*i.e.*, a subunit vaccine) produced in 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 ¶106.

In Trial 1, Blanchard administered DNA vaccines comprising plasmids encoding the ORF1 or ORF2 protein to piglets at 25 days of age, respectively. Ex.1003 ¶108. Two weeks later, Blanchard administered the same DNA vaccines and subunit vaccines containing a recombinant ORF1 or ORF2 protein expressed in a baculovirus system. Ex.1003 ¶108. Thus, a single dose of the recombinant ORF2 protein was administered as part of this second injection. Ex.1003 ¶108. Blanchard concluded that the recombinant ORF2 protein is the major immunogenic protein-inducing protective effect. Ex.1003 ¶109-110.

In Trial 2, Blanchard compared the efficacy of (i) a DNA vaccine containing both the ORF1 and ORF2 plasmids, and (ii) a subunit vaccine containing recombinant ORF1 and ORF2 proteins. Ex.1003 ¶111-112. While Blanchard ultimately administered two doses of this subunit vaccine, the data in Blanchard show seroconversion after just the first dose of the ORF2 subunit vaccine. Ex.1003 ¶113. The antibodies induced by that single dose were effective in neutralizing the PCV2 virus after challenge, suggesting that the antibodies were neutralizing antibodies. Ex.1003 ¶¶113-117. To the extent Patent Owner argues that Blanchard does not explicitly recognize this protective effect after a single dose, subsequent teachings (including the '872 Patent itself) recognize that a single dose of a composition containing the amount of ORF2 protein taught in Blanchard would inherently provide such a protective effect. *See supra* Claim 1.d.

1. Claim 1

1.a. "An immunogenic composition comprising:"

Blanchard teaches an immunogenic composition, *i.e.*, an ORF2 subunit vaccine that contains an antigen (ORF2 protein) and elicits an immune response. Ex.1003 ¶¶166-171. 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 ¶170. Blanchard also states that it "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 ¶171.

1.b. "an effective amount of recombinant PCV2 ORF2 protein."

Blanchard's ORF2 subunit vaccine comprised an effective amount of recombinant PCV2 ORF2 protein. Ex.1003 ¶172. Specifically, Blanchard ORF2 subunit vaccines (designated as "SU1 and SU2" in Table 2) comprise PCV2 ORF2 protein expressed recombinantly in baculovirus (designated "Orf2-vaccine group" in Table 1 and "Orf2/PCV2 - 5 x 10^6 cells" in Table 2). Ex.1006 at 4566-4577; Ex.1003 ¶¶173-178. 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 ¶179.

As discussed *infra* Claim 11, Patent-Owner's Principal Scientist alleges that Blanchard discloses the administration of between 106 and 169 μg of recombinant

ORF2 protein per dose. Ex.1003 ¶180. As discussed *supra* Section VIII.F.3, the '872 Patent states that ORF2 proteins is "effective in . . . very low concentrations, which means concentrations up to 0.25 µg/dose," and as such discloses that between 0.2 and 400 µg of recombinant ORF2 protein per dose is an effective amount. Ex.1003 ¶180. Finally, Petitioner's vaccine, Circumvent, contains significantly less than 106 µg of recombinant ORF2 protein per dose, and Patent-Owner contends that Circumvent meets this limitation. Ex.1003 ¶181. Thus, between 106 and 169 µg is an effective amount within the meaning of the claims. Ex.1003 ¶181.

1.c. "an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

Blanchard discloses an inactivated viral vector as an additional component of its ORF2 subunit vaccine. Ex.1003 ¶182. Specifically, Blanchard discloses the use of "[t]wo recombinant baculoviruses" containing the DNA for the ORF1 and ORF2 proteins. Ex.1006 at 4566; Ex.1003 ¶183. These baculoviruses are used to infect Sf9 cells, a type of insect cells, which then produce the ORF1 and ORF2 proteins. Ex.1003 ¶184. In order to release those proteins, the sf9 "cells were **lysed** by freezing at - 70 °C and thawing." Ex.1006 at 4566; Ex.1003 ¶185. This freeze-thaw cycle kills the Sf9 cells and inactivates at least some of the recombinant

baculoviruses, producing inactivated baculovirus vectors. Ex.1003 ¶186. Blanchard's ORF2 subunit vaccine was prepared from the lysate from these recombinant baculoviruses. Ex.1003 ¶187. This lysate, which is the fluid containing the contents of the lysed cells, contains inactivated baculovirus vectors; thus, the ORF2 subunit vaccine contains an inactivated viral vector. Ex.1003 ¶187.

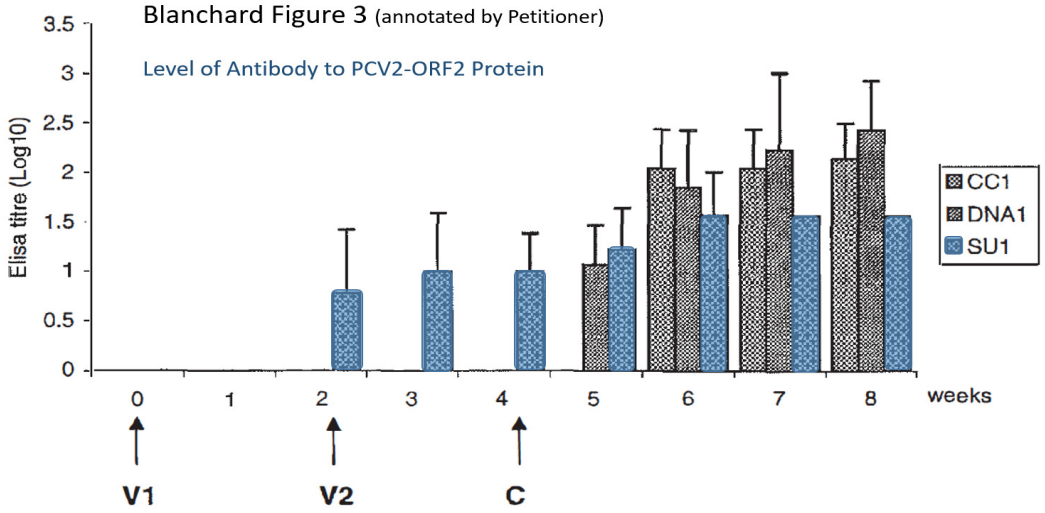
1.d. "said immunogenic composition provides a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose."

As discussed *supra* Claim 11, Blanchard's ORF2 subunit vaccine comprised between 106 and 169 μg of recombinant PCV2 ORF2 protein per dose. Ex.1003 ¶¶188-189. As explained in Section VI.E.2, the '872 Patent states that 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**," and that "recombinant baculovirus expressed PCV2 ORF2 protein is effective is [sic] in very low concentrations, which means concentrations up to 0.25 μg/dose." Ex.1001 at 22:52-56; Ex.1003 ¶189. The immunogenic response and resulting protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose of an immunogenic composition are inherent properties of that

composition. Ex.1003 ¶190. Accordingly, at the very least this element is inherently met by Blanchard's ORF2 subunit vaccine. *See supra* Section V.A.1; Ex.1003 ¶190.

Nonetheless, Blanchard discloses that the ORF2 subunit vaccine provides a protective effect against clinical symptoms associated with PCV2 infection after a single dose. First, in Trial 1, Blanchard administered a single dose of the ORF2 subunit vaccine as part of the second injection, and that single dose, together with other doses of the ORF2 DNA vaccine, provided a protective effect. Ex.1003 ¶191.

Second, in Trial 2, the first single dose of the ORF2 subunit vaccine induced a relatively high level of antibodies, and post-challenge results indicated that they were neutralizing antibodies. Ex.1003 ¶¶192-200. 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 ¶¶192-193. Figure 3 shows that seroconversion was detected two weeks after a single dose of the recombinant ORF2 vaccine, just before the second injection. Ex.1003 ¶194. 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, while seroconversion was only observed after challenge with the DNA vaccine." Ex.1003 ¶195.



Post-challenge results of Blanchard indicate 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 ¶196. Blanchard also found that the subunit vaccine protected against clinical symptoms associated with PCV2 infection after viral challenge. Ex.1003 ¶197. Specifically, Table 4 sets forth the "[c]linical protection of vaccinated groups after PCV2 challenge in trial no. 2" and lists "No" for "PMWS clinical symptoms" (i.e., clinical symptoms of PCV2 infection) for the ORF2 subunit vaccine group. Ex.1006 at 4570; Ex.1003 ¶197.

These results indicate that the first dose of Blanchard's ORF2 protein subunit vaccine induced the production of neutralizing antibodies. Ex.1003 ¶¶198-200. A neutralizing antibody is an antibody that defends a cell from an antigen by neutralizing the biological effect of that antigen. Ex.1003 ¶29. It was known that in order to protect against clinical symptoms associated with PCV2 infection, a sufficient level of neutralizing antibodies must be generated. Ex.1003 ¶198. Blanchard's ORF2 subunit vaccine clearly demonstrates antibody production after a single dose, and the subunit vaccine ultimately completely prevented clinical symptoms associated with PMWS. Ex.1003 ¶199. Therefore, the first dose of Blanchard's ORF2 subunit vaccine must have produced neutralizing antibodies. Ex.1003 ¶199. Indeed, 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 ¶200.

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 ¶201. 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 ¶201.

In view of these data, a POSA would recognize that a single dose of Blanchard's vaccine provided a protective effect against clinical symptoms associated with PCV2. Ex.1003 ¶202.

2. Claim 2

"The immunogenic composition of claim 1, wherein said PCV2 ORF2 protein is selected from the group consisting of:

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

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQID NO: 3 or SEQID NO: 4; and

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

As discussed *supra* Claim 1.b, Blanchard's ORF2 subunit vaccine comprised ORF2 proteins, or polypeptides. Ex.1003 ¶¶203-204. According to BLAST®, the sequence comparison tool identified in the '872 patent (Ex.1001 at 17:60-18:26), the

polypeptide of Blanchard (GenBank Accession No. AF201311) is 97% identical to the polypeptide of SEQ ID No. 3 of the '872 Patent, which is at least 90% homologous as set forth in element ii). Ex.1003 ¶¶204-207.

3. Claim 3

"The immunogenic composition of claim 1, wherein said composition further comprises an inactivated viral vector."

As discussed *supra* Claim 1.c, Blanchard discloses an inactivated viral vector as an additional component of its ORF2 subunit vaccine. Ex.1003 ¶¶208-209.

4. Claim 4

"The immunogenic composition of claim 3, wherein said inactivated viral vector is a recombinant baculovirus coding for the PCV2 ORF2 protein."

The recombinant baculovirus vector discussed *supra* Claim 3 codes for the PCV2 ORF2 protein. Ex.1003 ¶210. Specifically, Blanchard explains that the ORF2 gene (*i.e.*, the DNA sequence coding for PCV2 ORF2 protein) was cloned into a recombinant baculovirus vector. Ex.1006 at 4566; Ex.1003 ¶¶211-212. As explained *supra* Claim 1.c, the baculovirus vector is inactivated in the process of recovering the ORF2 protein, and is contained in the lysate that is ultimately used to make the vaccine. Ex.1003 ¶213. Thus, Blanchard's ORF2 subunit vaccine contains

an inactivated recombinant baculovirus coding for the PCV2 ORF2 protein. Ex.1003 ¶213.

5. Claim 5

"The immunogenic composition of claim 1, wherein said composition further comprises a component selected from the group consisting of cell culture Supernatant, Sodium thio-Sulfate, binary ethylenimine, carriers, adjuvants, media, diluents, isotonic agents, immunomodulatory agents, antibiotics, and combinations thereof."

Blanchard's ORF2 subunit vaccine contained at least an adjuvant. Ex.1003 ¶214. Table 2 of Blanchard shows that the subunit vaccine groups (SU1 and SU2) 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] was a 5x 10^6 lysed insect cells in Montanide which is a commercially available **oil-in-water adjuvant**."); Ex.1003 ¶¶215-216. As discussed *infra* Claim 21, Blanchard also discloses a carrier. Ex.1003 ¶217.

6. Claim 11

"The immunogenic composition of claim 1, wherein said immunogenic composition comprises 4-400 µg of recombinant PCV2 ORF2 protein."

Blanchard's ORF2 subunit vaccine comprised between 4-400 µg of recombinant PCV2 ORF2 protein. Ex.1003 ¶218. Specifically, Patent-Owner's Principal Scientist performed experiments to determine the "amount of PCV2 ORF2

protein present in the subunit vaccines which were generated and subsequently tested" in Blanchard, and determined that it "was **between 106 and 169 µg/dose**." Ex.1010 ¶¶2, 8; *see also* Ex.1009 at 22; Ex.1003 ¶¶219-221.

7. Claim 12

"The immunogenic composition of claim 1, wherein said immunogenic composition is a vaccine."

Blanchard's ORF2 subunit vaccine is a vaccine. Ex.1003 ¶222. For example, the Abstract of Blanchard states that "we have developed a specific PCV2 **vaccine** candidate," and, more specifically, that its study found that "protection induced by a **subunit vaccine** was even better than the one induced by DNA vaccine. . . ." Ex.1006 at Abstract; Ex.1003 ¶¶223. Patent-Owner admits that Blanchard discloses "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 ¶224.

8. Claim 13

"The immunogenic composition of claim 1, wherein the clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

Lung lesions, nasal shedding, cough, and diarrhea are all symptoms of PCV2 infection. Ex.1003 ¶¶225-226. Any vaccine that provides a protective effect against

the clinical symptoms associated with PCV2 infection will protect against these symptoms. Ex.1003 ¶227. Blanchard's ORF2 subunit vaccine, by providing a protective effect against clinical symptoms associated with PCV2 infection in a pig (*see supra* Claim 1.d), will necessarily provide a protective effect against these symptoms associated with PCV2 infection. Ex.1003 ¶228.

Indeed, Blanchard specifically discloses that "[c]linically, the disease [PMWS, or PCV2 infection] is characterized by pallor, fever and progressive wasting, together with **respiratory and digestive disorders**." Ex.1006 at 4565; Ex.1003 ¶229. Lung lesions, nasal shedding, and cough are respiratory disorders; diarrhea is a digestive disorder. Ex.1003 ¶230. Table 4 sets forth the "[c]linical protection of vaccinated groups after PCV2 challenge in trial no. 2" and lists "No" for "PMWS clinical symptoms" (*i.e.*, clinical symptoms associated with PCV2 infection) for the ORF2 subunit vaccine group. Ex.1006 at 4570; Ex.1003 ¶¶231-232. Thus, Blanchard explicitly discloses that its ORF2 subunit vaccine protected against, among other things, respiratory and digestive disorders, including lung lesions, nasal shedding, cough, and diarrhea. Ex.1003 ¶233.

In sum, not only does Blanchard disclose a vaccine that inherently protects against lung lesions, nasal shedding, cough and diarrhea, Blanchard explicitly

discloses that the piglets receiving the ORF2 subunit vaccine did not show these symptoms. Ex.1003 ¶234.

9. Claim 14

"The immunogenic composition of claim 1, wherein said dose of said immunogenic composition is formulated to have a volume of at least 1 ml."

Blanchard's ORF2 subunit vaccine is formulated to have a volume of 2 mL, which is at least 1 mL. Ex.1003 ¶235. Specifically, Blanchard explains that the "subunit vaccine was prepared in a **total volume of 2 ml**, 1 ml of cells in PBS pH 7.2 mixed with 1 ml of a water-in-oil adjuvant (Montanide)." Ex.1006 at 4657. Ex.1003 ¶236.

10. Claim 15

"A method of providing a protective effect against clinical symptoms of PCV2 infection in a pig after administration of a single dose of an immunogenic composition comprising the step of: administering said immunogenic composition to said pig, wherein said immunogenic composition comprises an effective amount of recombinant PCV2 ORF2 protein selected from the group consisting of:

i) 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;

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 4; and

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

As discussed *supra* Claim 1, Blanchard's ORF2 subunit vaccine comprises an effective amount of a recombinant PCV2 ORF2 protein that provides a protective effect against clinical symptoms of PCV2 infection in a pig after a single dose. Ex.1003 ¶238. Blanchard discloses a method of administering these vaccines, and thus discloses a method of providing a protective effect against clinical symptoms associated with PCV2 infection in a pig after a single dose. Ex.1003 ¶¶239-240. Finally, as discussed *supra* Claim 2, Blanchard's ORF2 subunit vaccine comprises PCV2 ORF2 protein selected from the group consisting of elements (i) to (iv) of Claim 15. Ex.1003 ¶242.

Thus, Blanchard discloses all elements of Claim 15. Ex.1003 ¶237.

11. Claim 16

"The method of claim 15, wherein said clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

As discussed *supra* Claim 13, Blanchard's ORF2 subunit vaccine, by providing a protective effect against clinical symptoms of PCV2 infection in a pig,

will necessarily provide a protective effect against lung lesions, nasal shedding, cough, diarrhea, and combinations thereof, which are all clinical symptoms of PCV2 infection. Ex.1003 ¶¶244. Furthermore, Blanchard explicitly discloses that the piglets receiving the ORF2 subunit vaccine did not show these symptoms. *See supra* Claim 13. Ex. 1003 ¶244. Blanchard discloses methods of administering its vaccine, and therefore discloses a method of providing a protective effect against these symptoms associated with PCV2 infection after a single dose. Ex.1003 ¶243, 245.

12. Claim 18

"The method of claim 15, wherein said immunogenic composition is administered intramuscularly, subcutaneously, intranasally, orally, or any combination thereof."

Blanchard discloses that the ORF2 subunit vaccine was injected intramuscularly in Trials 1 and 2, respectively. Ex.1006 at 4566 (Trial 1) (injection "on one side of the neck"), 4567 (Trial 2) ("a first **intramuscular** injection of baculovirus-expressed protein emulsion"); Ex.1003 ¶¶246-247.

13. Claim 19

"The method of claim 15, wherein said effective amount of recombinant PCV2 ORF2 is at least 4 µg."

As discussed *supra* Claim 11, Blanchard's ORF2 subunit vaccine comprised between 106 and 169 µg of recombinant PCV2 ORF2 protein per dose, which is at least 4 µg. Ex.1003 ¶¶248-249.

14. Claim 20

20.a. "An immunogenic composition comprising."

As discussed *supra* Claim 1.a, Blanchard discloses an immunogenic composition. Ex.1003 ¶250.

20.b. "at least 2 µg of recombinant PCV2 ORF2 protein."

As discussed *supra* Claim 11, Blanchard's ORF2 subunit vaccine comprised between 106 and 169 µg of recombinant PCV2 ORF2 protein per dose, which is at least 2 µg. Ex.1003 ¶¶251-252.

20.c. "and an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

As discussed *supra* Claim 1.c, Blanchard discloses an inactivated viral vector as an additional component of its ORF2 subunit vaccine. Ex.1003 ¶¶253-254.

20.d. "wherein said immunogenic composition provides a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose thereof."

As discussed *supra* Claim 1.d, Blanchard's ORF2 subunit vaccine provided a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose. Ex.1003 ¶¶255-256.

15. Claim 21

"An immunogenic composition comprising:

An effective amount of recombinant PCV2 ORF2 protein and a carrier, wherein said PCV2 ORF2 protein is selected from the group consisting of:

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

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQID NO: 3 or SEQID NO: 4; and

iv) any polypeptide that is encoded by a polynucleotide that is at least 90% homologous to the polynucleotide of iii.

Wherein said immunogenic composition provides a protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof."

As discussed *supra* Claims 1 and 2, Blanchard's ORF2 subunit vaccine comprised an effective amount of recombinant PCV2 ORF2 protein that provides a

protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof, wherein the PCV2 ORF2 protein is selected from the groups set forth in elements (i) to (iv) of Claim 21. Ex.1003 ¶¶257-258.

Blanchard also discloses an immunogenic composition comprising a carrier, specifically, a diluent. Ex.1003 ¶259. The '872 Patent defines "a pharmaceutical-acceptable carrier" as "any and all solvents, dispersion media, coatings, stabilizing agents, **diluents**, preservatives, antibacterial and antifungal agents, isotonic agents, adsorption delaying agents, and the like." Ex.1001 at 15:16-21; Ex.1003 ¶260. It states that "**Diluents** can include water, **saline**, dextrose, ethanol, glycerol, and the like." Ex.1001 at 21:42-43; Ex.1003 ¶260. Blanchard discloses 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.1003 ¶261. **PBS** (Phosphate Buffered **Saline**) is a diluent as defined by the '872 Patent. Ex.1003 ¶261.

16. Claim 22

"The immunogenic composition of claim 21, wherein said composition further comprises an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

As discussed *supra* Claim 1.c, Blanchard discloses an inactivated viral vector as an additional component of its ORF2 subunit vaccine. Ex.1003 ¶¶262-263.

17. Claim 23

"The immunogenic composition of claim 21, wherein said effective amount of recombinant PCV2 ORF2 protein is between 4-400 µg."

As discussed *supra* Claim 11, Blanchard's ORF2 subunit vaccine comprised between 106 and 169 µg of recombinant PCV2 ORF2 protein per dose, which is between 4-400 µg. Ex.1003 ¶¶264-265.

18. Claim 24

"The immunogenic composition of claim 21, wherein the clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

As discussed *supra* Claim 21, Blanchard's ORF2 subunit vaccine provided a protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof. Ex.1003 ¶267. As discussed *supra* Claim 13, Blanchard's ORF2 subunit vaccine, by providing a protective effect against clinical symptoms of PCV2 infection in a pig, will necessarily provide a protective effect against lung lesions, nasal shedding, cough, diarrhea, and combinations thereof, which are all clinical symptoms of PCV2 infection. Ex.1003 ¶268. Thus, Blanchard discloses the immunogenic composition of claim 21, where the clinical

symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea and combinations thereof. Ex.1003 ¶¶266, 268.

C. GROUND 2: CLAIMS 1-5, 11-13, 15-16 AND 18-24 ARE ANTICIPATED UNDER §102(B) BY JESTIN

Jestin describes 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. Example 8 of Jestin discloses a single dose of an ORF2 protein subunit vaccine administered as the third injection of a prime-boost protocol. Ex.1003 ¶¶104-105. That single dose of ORF2 protein, together with other doses of the ORF2 *DNA* vaccine, provided a protective effect against clinical symptoms associated with PCV2 infection. Ex.1003 ¶¶104-105.

To the extent Patent-Owner argues that Jestin does not explicitly recognize that the Example 8 ORF2 subunit vaccine provided a protective effect after a single dose, subsequent teachings (including the '872 Patent itself) recognize that a single dose of a composition containing the amount of ORF2 protein taught in Jestin would inherently provide such a protective effect.

1. Claim 1

1.a. "An immunogenic composition comprising:"

Jestin discloses immunogenic compositions, i.e., ORF2 subunit vaccines, that contain an antigen (ORF2 protein) that elicits an immune response. Ex.1003 ¶¶271-273. *See also, 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 circovirus, especially of type B [i.e., PCV2]."); *id.* Cl. 5; Ex.1009 at 11; Ex.1003 ¶¶274-276.

1.b. "an effective amount of recombinant PCV2 ORF2 protein."

Jestin discloses vaccines comprising an effective amount of recombinant PCV2 ORF2 protein. Ex.1003 ¶277. Specifically, Jestin teaches a vaccine comprising the protein encoded by DNA SEQ ID No. 25. Ex.1005 at 3:52-67; Ex.1003 ¶278. 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 281; Ex.1003 ¶¶279-281. Jestin teaches that the ORF2 protein of SEQ ID No. 26 may be prepared "in recombinant form," *see, e.g.*, Ex.1005 at 18:1-7, 18:20-27, which is then used as "an immunogenic and/or vaccine composition" comprising recombinant ORF2 protein (*i.e.*, "a polypeptide of sequence . . . SEQ ID No. 26"),

id. at 24:61-67; Ex.1003 ¶¶282-284. Patent-Owner admits 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 ¶285.

Jestin discloses the use of this recombinant ORF2 protein in an effective amount. 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 circovirus." Ex.1005 at 25:63-26:1; Ex.1003 ¶286. In particular, in Example 8, piglets received an injection of a vaccine composition comprising "the **ORF2 recombinant protein**." Ex.1005 at 47:12-18; Ex.1003 ¶¶287-289. Jestin concludes that "[e]xpression of [PCV2] **ORF2** [protein]. . . in swine **resulted in a significantly enhanced level of protection** as evaluated by weight evolution and body temperature evolution following challenge with [PCV2] circovirus." Ex.1005 at 47:51-54; Ex.1003 ¶290. In other words, the recombinant ORF2 protein resulted in a significantly enhanced protective effect against symptoms of PCV2 infection, and thus the amount of recombinant ORF2 protein was "effective." Ex.1003 ¶¶290-291.

Finally, as discussed *infra* Claim 11, Patent-Owner has taken the position that Jestin's ORF2 vaccines comprised between 63.3 and 271.4 μg of recombinant PCV2

ORF2 protein per dose, which is an effective amount according to the '872 Patent. *See supra* Section VII.B, Claim 1.b; Ex.1003 ¶¶292-293. Furthermore, Petitioner's vaccine, Circumvent, contains significantly less than 63.3 μg of recombinant ORF2 protein per dose, and Patent-Owner contends that Circumvent meets this limitation. Ex.1003 ¶293.

1.c. "an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

Jestin discloses an inactivated viral vector as an additional component of its ORF2 vaccine. Ex.1003 ¶294. For example, in Example 8, "[t]he ORF1-encoded protein (REP) and **ORF2-encoded putative capsid protein of PCV-B** were expressed . . . in insect cells by **recombinant baculovirus vectors** . . . ." Ex.1005 at 47:8-13; Ex.1003 ¶295. Jestin also teaches "recovery of [these] recombinant polypeptide[s]." Ex.1005 at 18:21-26; Ex.1003 ¶296. In order to recover the ORF2 proteins to use them in the vaccine, the cells containing them must be lysed, which inactivates at least some of the recombinant baculovirus vector. Ex.1003 ¶¶297-298.

1.d. "said immunogenic composition provides a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose."

As discussed *infra* Claim 11, Jestin's ORF2 subunit vaccine comprised between 63.3 and 271.4 μg of recombinant PCV2 ORF2 protein per dose. Ex.1003 ¶¶299-300. As explained in Section VI.E.2, the '872 Patent states that a concentration of ORF2 protein as low as 0.2 μg per dose is a "effective for inducing the desired immune response, namely **reducing the incidence of or lessening the severity of clinical signs resulting from PCV2 infection**," and that "recombinant baculovirus expressed PCV2 ORF2 protein is effective is [sic] in very low concentrations, which means concentrations up to 0.25 μg/dose." Ex.1001 at 22:52-56; Ex.1003 ¶300. The immunogenic response and resulting protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose of an immunogenic composition is an inherent property of that composition. Ex.1003 ¶301. Accordingly, at the very least, this element is inherently met by Jestin's ORF2 subunit vaccine. *See supra* Section V.A.1; Ex.1003 ¶301.

In addition to the inherent disclosure, Jestin expressly teaches that its ORF2 vaccines "will be administered **one time** or several times," and that "the vaccine of the present invention is administered in an amount that **is protective against piglet**

weight loss disease." Ex.1005 at 27:39-46; Ex.1003 ¶302. Thus, this element is both inherently and expressly disclosed in Jestin. Ex.1003 ¶302.

Moreover, in Example 8, Jestin administered a DNA vaccine comprising DNA plasmids encoding ORF2 protein (first injection), and two weeks later, the same DNA vaccine and a subunit vaccine containing a recombinant ORF2 protein expressed in a baculovirus system (second and third injections). Ex.1003 ¶303. After challenge with PCV2, the pigs had a significant level of protection against PCV2 disease. Ex.1003 ¶304. Jestin thus showed that a single dose of the ORF2 subunit vaccine, together with other doses of the ORF2 DNA vaccine, provided a protective effect against clinical symptoms associated with PCV2 infection. Ex.1003 ¶304.

2. Claim 2

"The immunogenic composition of claim 1, wherein said PCV2 ORF2 protein is selected from the group consisting of:

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

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQID NO: 3 or SEQID NO: 4; and

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

As discussed *supra* Claim 1.b, Jestin teaches an immunogenic composition comprising the polypeptide in SEQ ID No. 26, *i.e.*, the ORF2 protein. Ex.1005 at 3:52-67, 11:8-38:22-24; Ex.1003 ¶306. 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 '872 Patent, which is at least 90% homologous as set forth in element ii). Ex.1003 ¶¶305, 307-310.

3. Claim 3

"The immunogenic composition of claim 1, wherein said composition further comprises an inactivated viral vector."

As discussed *supra* Claim 1.c, Jestin discloses an inactivated viral vector as an additional component of its ORF2 vaccine. Ex.1003 ¶¶311-312.

4. Claim 4

"The immunogenic composition of claim 3, wherein said inactivated viral vector is a recombinant baculovirus coding for the PCV2 ORF2 protein."

The recombinant baculovirus vector discussed *supra* Claim 3 codes for the PCV2 ORF2 protein. Ex.1003 ¶314. In the section of Example 8 entitled "Construction of Recombinant Baculoviruses," Jestin explains that "ORF2 proteins were expressed," and the "recombinant proteins were detected by western-blot using

swine polyclonal antibodies." Ex.1005 at 47:38-40; Ex.1003 ¶314. In order to express recombinant ORF2 protein, the recombinant baculovirus must "code for" the ORF2 protein. Ex.1003 ¶315.

As discussed *supra* Claim 1.c, these recombinant baculoviruses are inactivated in the immunogenic composition, because they are inactivated during the process of recovering the protein. Ex.1003 ¶316. Thus, Jestin discloses the immunogenic composition of claim 3, wherein the inactivated viral vector is a recombinant baculovirus coding for the PCV2 ORF2 protein. Ex.1003 ¶313.

5. Claim 5

"The immunogenic composition of claim 1, wherein said composition further comprises a component selected from the group consisting of cell culture Supernatant, Sodium thio-Sulfate, binary ethylenimine, carriers, adjuvants, media, diluents, isotonic agents, immunomodulatory agents, antibiotics, and combinations thereof."

Jestin teaches that "[i]n one embodiment of the invention, the nucleotide sequence is . . . SEQ ID No. 25 . . . . In yet another embodiment, **the vaccines further comprising [sic] an adjuvant.**" Ex.1005 at 3:44-51; Ex.1003 ¶¶317-318. Jestin also states 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.* 27:19-25 (listing

several examples of "**adjuvants** of the appropriate immunity which are known to the person skilled in the art"). Ex.1003 ¶¶319-320. Finally, Patent-Owner admits that "Jestin discloses that the vaccine may be combined with **one or more adjuvants.**" Ex.1009 at 18; Ex.1003 ¶321.

As discussed *infra* Claim 21, Jestin also discloses the use of a carrier. Ex.1003 ¶322.

6. Claim 11

"The immunogenic composition of claim 1, wherein said immunogenic composition comprises 4-400 µg of recombinant PCV2 ORF2 protein."

Jestin's vaccines comprise between 4-400 µg of recombinant PCV2 ORF2 protein. Ex.1003 ¶323. Jestin teaches vaccines comprising ORF2 "in an amount of about 0.1 to 10 µg polypeptide per kilogram weight of the animal," Ex.1005 at 27:42-49, and teaches administration of the vaccine to five-week-old piglets, *id.* 38:58-65, 47:24-44; Ex.1003 ¶¶324-325. Five-week-old piglets weigh about 10 kg. Ex.1003 ¶326. At that weight, Jestin's vaccines contain up to 100 µg of recombinant PCV2 ORF2 protein. Ex.1003 ¶327. Patent-Owner states that 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"—all of which are

well within the claimed 4-400 μg range. Ex.1010 at 14; Ex.1003 ¶328. Thus, Jestin discloses this limitation. Ex.1003 ¶329.

7. Claim 12

"The immunogenic composition of claim 1, wherein said immunogenic composition is a vaccine."

Jestin's ORF2 protein vaccine is a vaccine. Ex.1003 ¶¶330-331. Jestin states that its "invention relates to **vaccines** comprising a pharmaceutically acceptable vehicle and a single polypeptide, wherein the single polypeptide consists of SEQ ID No. 26 [the sequence for ORF2.]" Ex.1005 at 1:17-19; *see also id.* Cl. 5. Ex.1003 ¶332. For example, Example 8 of Jestin contains a section "**Vaccination** and Challenge," which explains that "[f]our groups of 7 pigs were **vaccinated** intramuscularly . . . ." Ex.1005 at 37:45-49; Ex.1003 ¶334.

8. Claim 13

"The immunogenic composition of claim 1, wherein the clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

Lung lesions, nasal shedding, cough, and diarrhea are all symptoms of PCV2 infection. Ex.1003 ¶336. Any vaccine that provides a protective effect against the clinical symptoms associated with PCV2 will protect against these symptoms. Ex.1003 ¶336. Jestin's ORF2 vaccines, by providing a protective effect against

clinical symptoms associated with PCV2 infection in a pig (*see supra* Claim 1.d), will necessarily provide a protective effect against these symptoms associated with PCV2 infection. Ex.1003 ¶¶335, 337.

9. Claim 15

"A method of providing a protective effect against clinical symptoms of PCV2 infection in a pig after administration of a single dose of an immunogenic composition comprising the step of: administering said immunogenic composition to said pig, wherein said immunogenic composition comprises an effective amount of recombinant PCV2 ORF2 protein selected from the group consisting of:

i) 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;

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 4; and

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

As discussed *supra* Claim 1, Jestin's ORF2 vaccines comprise an effective amount of a recombinant PCV2 ORF2 protein that provides a protective effect against clinical symptoms of PCV2 infection in a pig after a single dose. Ex.1003 ¶339. Jestin discloses methods of administering these vaccines, and therefore

discloses a method of providing a protective effect against clinical symptoms of PCV2 infection in a pig after a single dose. Ex.1005 at 27:39-46 ("the polypeptide will be **administered one time**"), 47:1-67 (Example 8); *see also id.* Cls. 5-8, 11-12 (reciting "**method[s]** of **immunizing** a mammal **against piglet weight loss disease**"); Ex.1009 at 11 (stating that "Jestin discloses" "a method for the protection of piglets"); Ex.1003 ¶¶340-342 As discussed *supra* Claim 2, Jestin's ORF2 vaccines comprise PCV2 ORF2 protein selected from the group consisting of elements (i) to (iv) of Claim 15. Ex.1003 ¶343.

Thus, Jestin discloses all elements of Claim 15. Ex.1003 ¶338.

10. Claim 16

"The method of claim 15, wherein said clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

As discussed *supra* Claim 13, Jestin's ORF2 vaccines, by providing a protective effect against clinical symptoms of PCV2 infection in a pig, will necessarily provide a protective effect against lung lesions, nasal shedding, cough, diarrhea, and combinations thereof, which are all clinical symptoms of PCV2 infection. Ex.1003 ¶¶344-345.

11. Claim 18

"The method of claim 15, wherein said immunogenic composition is administered intramuscularly, subcutaneously, intranasally, orally, or any combination thereof."

The piglets of Example 8 of Jestin "were vaccinated **intramuscularly**." Ex.1005 at 47:42-43; Ex.1003 ¶¶346-347.

12. Claim 19

"The method of claim 15, wherein said effective amount of recombinant PCV2 ORF2 is at least 4 µg."

As discussed *supra* Claim 11, Jestin's ORF2 vaccines comprised up to 100 µg of recombinant PCV2 ORF2 protein per dose, which is at least 4 µg. Ex.1003 ¶¶348-349.

13. Claim 20

20.a. "An immunogenic composition comprising."

As discussed *supra* Claim 1.a, Jestin discloses the administration of immunogenic compositions of PCV2 ORF2 proteins. Ex.1003 ¶350.

20.b. "at least 2 µg of recombinant PCV2 ORF2 protein."

As discussed *supra* Claim 11, Jestin's ORF2 vaccines comprised between 63.3 and 271.4 µg of recombinant PCV2 ORF2 protein per dose, which is at least 2 µg. Ex.1003 ¶¶351-352.

20.c. "and an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

As discussed *supra* Claim 1.c, Jestin discloses an inactivated viral vector as an additional component of its ORF2 vaccine. Ex.1003 ¶¶353-354.

20.d. "wherein said immunogenic composition provides a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose thereof."

As discussed *supra* Claim 1.d, Jestin's ORF2 vaccines provide a protective effect against clinical symptoms associated with a PCV2 infection after administration of a single dose. Ex.1003 ¶¶355-356.

14. Claim 21

"An immunogenic composition comprising:

An effective amount of recombinant PCV2 ORF2 protein and a carrier, wherein said PCV2 ORF2 protein is selected from the group consisting of:

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

ii) any polypeptide that is at least 90% homologous to the polypeptide of i);

iii) a polypeptide that is encoded by a DNA comprising the sequence of SEQID NO: 3 or SEQID NO: 4; and

iv) any polypeptide that is encoded by a polynucleotide that is at least 90% homologous to the polynucleotide of iii.

Wherein said immunogenic composition provides a protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof."

As discussed *supra* Claims 1 and 2, Jestin's ORF2 vaccines comprise an effective amount of recombinant PCV2 ORF2 protein that provides a protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof, wherein the PCV2 ORF2 protein is selected from the groups set forth in elements (i) to (iv) of Claim 21. Ex.1003 ¶358.

Jestin also discloses an immunogenic composition comprising a carrier. Ex.1003 ¶359. The '872 Patent defines "a pharmaceutical-acceptable carrier" as "any and all solvents, dispersion media, coatings, stabilizing agents, **diluents**, preservatives, antibacterial and antifungal agents, isotonic agents, adsorption delaying agents, and the like." '872 Patent 15:16-21; Ex.1003 ¶360. Jestin states that its "invention relates to vaccines comprising a **pharmaceutically acceptable vehicle** and [the ORF2 polypeptide]" Ex.1005 at 4:14-17, and stabilizing agents, antifungal agents, diluents and preservatives, are all pharmaceutically acceptable vehicles. Ex.1003 ¶¶361-362. In addition, Example 5 of Jestin discloses the use of "PBS," Phosphate Buffered Saline, which is a saline diluent, and thus a carrier as defined by the '872 Patent. Ex.1003 ¶363.

15. Claim 22

"The immunogenic composition of claim 21, wherein said composition further comprises an additional component selected from the group consisting of viral inactivators, inactivated viral vector, viral inactivator neutralizers, and combinations thereof."

As discussed *supra* Claim 1.c, Jestin discloses an inactivated viral vector as an additional component of its ORF2 vaccine. Ex.1003 ¶¶364-365.

16. Claim 23

"The immunogenic composition of claim 21, wherein said effective amount of recombinant PCV2 ORF2 protein is between 4-400 µg."

As discussed *supra* Claim 11, Jestin's ORF2 vaccines comprised between 63.3 and 271.4 µg of recombinant PCV2 ORF2 protein per dose, which is between 4-400 µg. Ex.1003 ¶¶366-367.

17. Claim 24

"The immunogenic composition of claim 21, wherein the clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof."

As discussed *supra* Claim 21, Jestin's ORF2 vaccines provide a protective effect against clinical symptoms associated with PCV2 infection after administration of a single dose thereof. Ex.1003 ¶369. As discussed *supra* Claim 13, Jestin's ORF2 vaccines, by providing a protective effect against clinical symptoms of PCV2

infection in a pig, will necessarily provide a protective effect against lung lesions, nasal shedding, cough, diarrhea, and combinations thereof, which are all clinical symptoms of PCV2 infection. Ex.1003 ¶370. Thus, Jestin discloses the immunogenic composition of claim 21, wherein the clinical symptoms are selected from the group consisting of lung lesions, nasal shedding, cough, diarrhea, and combinations thereof. Ex.1003 ¶368.

D. GROUND 3: CLAIMS 1-5, 11-16, AND 18-24 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* Ground 1, and incorporated here by reference, Blanchard anticipates Claims 1-5, 10-16, and 18-24 of the '872 Patent, and Jestin anticipates Claims 1-5, 11-13, 15-16 and 18-24. To the extent Patent-Owner argues that Blanchard and Jestin do not teach the administration of an ORF2 vaccine that provides a protective effect against clinical symptoms after administration of a single dose, that limitation is obvious to a POSA over Blanchard, in further view of Jestin, Meng, and Fenaux.

Meng describes the immunogenicity of the recombinant PCV2 ORF2 protein, and teaches the use of a chimeric virus, PCV1-2, containing that protein, both live and inactivated, as a single-dose vaccine. Ex.1003 ¶372. The data in Meng show the

administration of a single dose of PCV1-2 DNA vector induces the production of antibodies to ORF2. Ex.1003 ¶372. Fenaux confirms that these antibodies protect against PCV2 infection by providing data demonstrating that a single dose of the live PCV1-2 virus provides a protective effect against clinical symptoms associated with PCV2 infection. Ex.1003 ¶373. While Fenaux's PCV1-2 virus was not inactivated, a POSA would have been motivated by the express teaching in Meng to inactivate the PCV1-2 virus, and because inactivated vaccines are safer and more stable than live vaccines, amongst other reasons. Ex.1003 ¶¶373-380.

1. Motivation to Combine

A POSA would have been motivated to combine the teachings of Blanchard, Jestin, Meng, and Fenaux. Ex.1003 ¶381. First, all of these references teach immunogenic compositions containing PCV2 ORF2 protein to protect against PCV2 infection. Ex.1003 ¶381. Meng and Fenaux teach single-dose immunogenic compositions comprising the PCV1-2 virus, which comprises the ORF2 protein as its antigenic component, with Fenaux confirming that a single dose of a live PCV1-2 virus provides a protective effect against symptoms associated with PCV2 infection. Ex.1003 ¶382. As discussed *supra* Sections VII.B & C, both Blanchard and Jestin teach subunit vaccines that contain an effective amount of ORF2 protein,

with Blanchard providing data demonstrating that a single dose of the ORF2 subunit vaccine provides a protective effect against symptoms associated with PCV2 infection. Ex.1003 ¶383.

A POSA would be motivated to combine Meng and Fenaux's teaching of administering the PCV1-2 virus in a single-dose regimen with Blanchard and Jestin's PCV2 ORF2 subunit vaccines, to **administer an ORF2 subunit vaccine in a single-dose regimen**. Ex.1003 ¶384. 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 ¶¶385-386.

Moreover, it was well-known 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 ¶¶387-388. Thus, a POSA would be motivated to administer a ORF2 protein-VLP vaccine and could reasonably expect that a single dose ORF2 subunit vaccine would provide at

least some degree of protective effect similar to that observed for the single dose of PCV1-2 vaccine in Fenaux. Ex.1003 ¶¶389-391.

In addition, a POSA would be highly motivated to create a single-dose vaccine for PCV2. Ex.1003 ¶¶392-393. 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 ¶393. 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.
>
> Hayes Decl. ¶13; Ex.1003 ¶¶394-395.

Thus, a POSA would have been motivated to combine Meng 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 and Jestin's subunit vaccines are structurally similar to Meng and Fenaux's PCV1-2 virus, but provide a safer and more commercially viable option. Ex.1003 ¶396.

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 ¶397.

Both Blanchard and Jestin teach subunit vaccines comprising an amount of recombinant PCV2 ORF2 protein within the dosage range taught in the '872 Patent. *Supra* Section VII.B&C, Claim 1.b; Ex.1003 ¶398. Jestin discloses a single dose of the ORF2 subunit vaccine. *Supra* Section VII.C. Claim 1.d; Ex.1003 ¶399. And the data in Blanchard demonstrate that within 14 days of a single dose of the subunit vaccine the piglets seroconverted (*i.e.*, developed antibodies). *Supra* Section VII.B, Claim 1.d; Ex.1003 ¶400. The antibodies induced by the recombinant ORF2 protein were effective in neutralizing the PCV2 virus and preventing clinical symptoms after challenge, indicating that the first dose of Blanchard's ORF2 subunit vaccine

induced the production of neutralizing antibodies. *Id*. Furthermore, the level of antibodies induced by the first dose of Blanchard's ORF2 subunit vaccine was roughly the same as the level that was ultimately able to "provide significant protection against PCV2 infection" after two injections. *Id.*

Meng teaches that a PCV1-2 DNA vector, a live or inactivated PCV1-2 virus, and an ORF2 subunit vaccine (all of which contain ORF2 protein as their immunogenic component) may be administered as single-dose vaccines to protect pigs against PCV2 infection or PMWS. Ex.1003 ¶401. It further discloses data demonstrating that a single dose of chimeric PCV1-2 DNA vector, which produces ORF2 protein through expression, induces the creation of antibodies specific to ORF2 protein. Ex.1003 ¶401.

Fenaux discloses data demonstrating the efficacy of live PCV1-2 virus, which contains ORF2 protein as its antigenic component, as a single-dose vaccine. Ex.1003 ¶402. This single dose of ORF2 protein induced the production of antibodies to ORF2 protein in all 12 piglets studied at 42 days post-vaccination. Ex.1003 ¶402. Fenaux further teaches that these ORF2 antibodies are sufficient to provide protective effects against clinical symptoms associated with PCV2 after just a single dose of the PCV1-2 virus. Ex.1003 ¶402.

In view of the data in Blanchard alone, and further in view of Meng and Fenaux, a POSA would have had more than a reasonable expectation that a single-dose recombinant ORF2 subunit vaccines would provide a protective effect against 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 dosage range taught in the '872 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 and Fenaux's PCV1-2 virus were specific to the same protein, ORF2 protein; and (5) 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 ¶403.

Moreover, as of December 2004 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 ¶¶404-412. Furthermore, several inactivated vaccines were commercially available for single-dose administration at that time. Ex.1003 ¶413.

The fact that Blanchard teaches that its data predict good efficacy for a ORF2 vaccine "in a prime-boost approach," Ex.1006 at 4574, does not make the use of such vaccines in a single-dose regimen any less obvious. At most, it suggests that the authors of Blanchard may have preferred a two-dose regimen. *See Bayer Pharma AG v. Watson Laboratories, Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017) ("[T]he fact that there may be reasons a skilled artisan would prefer one [approach] over the other does ***not*** amount to a teaching away from the lesser preferred but still workable option") (emphasis added). And, as explained above, single-dose regimens were specifically taught in Meng and Fenaux, generally preferred amongst artisans, and a POSA would reasonably expect that approach to be successful here. Accordingly, the combination of Blanchard and Jestin's recombinant ORF2 subunit vaccines with the single-dose regimen in Meng and Fenaux renders claims 1-5, 10-16 and 18-24 obvious.

E. GROUND 4: CLAIMS 6-10 ARE OBVIOUS UNDER §103(A) OVER BLANCHARD AND JESTIN IN VIEW OF THE KNOWLEDGE OF A POSA, AND ALSO IN VIEW OF BUBLOT

To the extent Patent-Owner contends that certain additional elements required of the vaccine formulations in claims 6-10 are not taught by the references in grounds 1, 2, and 3, those limitations are taught by Bublot and were within the knowledge of a POSA, and thus those claims are obvious in further view of the same.

Bublot is prior art under 35 U.S.C. §102(b). Ex.1003 ¶414. It teaches immunogenic compositions containing vectors that express ORF2 protein and that confer protective immunity against PCV2 infection, as well as methods for administering those compositions. Ex.1003 ¶414. A POSA would be motivated to combine Bublot, Blanchard, and Jestin because all of these references relate to vaccines to prevent PCV2 infection that comprises recombinant ORF2 proteins, and the additional ingredients taught in Bublot were routinely used for the purpose of improving vaccine formulations. Ex.1003 ¶415. A POSA would have a reasonable expectation of success in using the vaccine ingredients disclosed in Bublot in the vaccines of Blanchard and Jestin, as the use of such ingredients was well-known and routine in the art as of 2004. Ex.1003 ¶¶416-418.

1. Claim 6

"The immunogenic composition of claim 5, wherein said adjuvant is selected from the group consisting of acrylic acid, methacrylic acid, and any polymer thereof."

Bublot discloses a PCV2 vaccine "contain[ing] at least one adjuvant compound chosen from the **polymers of acrylic or methacrylic acid** and the copolymers of maleic anhydrive and alkenyl derivative," adjuvants that were well-known to a POSA. Ex.1012 at 6:64-67; Ex.1003 ¶420. As discussed *supra* Sections VII.B & C, Claim 5, Blanchard and Jestin teach vaccines containing an adjuvant. Ex.1003 ¶421. The use of adjuvants to enhance the immunogenic effect of a vaccine was well-known to a POSA. *Supra* Section VII.C, Claim 5; Ex.1003 ¶422. Thus, it would have been obvious to a POSA to administer those vaccines with a well-known adjuvant such as acrylic acid, methacrylic acid, or a polymer thereof, as disclosed in Bublot and as known by a POSA. Ex.1003 ¶¶419, 423.

2. Claim 7

"The immunogenic composition of claim 6, wherein said adjuvant is a polymer of an acrylic or methacrylic acid and wherein said polymer is cross-linked with polyalkenyl ethers of sugars or polyalcohols."

3. Claim 8

"The immunogenic composition of claim 1, wherein said composition further comprises a carbomer."

Bublot teaches that "[t]he preferred adjuvant compounds are the **polymers of acrylic or methacrylic acid which are cross-linked, especially with polyalkenyl ethers of sugars or polyalcohols**. These compounds are known by the term carbomer." Bublot 7:1-4; Ex.1003 ¶425. The use of these carbomers to enhance the immunogenic effect of a vaccine was well-known to a POSA. Ex.1003 ¶426. As discussed *supra* Claim 6, Blanchard and Jestin teach vaccines containing an adjuvant. Ex.1003 ¶427. Thus, it would have been obvious to a POSA to use a polymer of an acrylic or methacrylic acid that is cross-linked with polyalkenyl ethers of sugars or polyalcohols, or a carbomer, as taught in Bublot, as the adjuvant in Blanchard and Jestin's vaccines. Ex.1003 ¶¶424, 428.

4. Claim 9

"The immunogenic composition of claim 8, wherein said carbomer is present in an amount of about 500 µg to about 5 mg carbomer per dose."

Bublot teaches an immunogenic composition containing between 500 µg to about 5 mg of Carbopol,™ which is a carbomer. Ex.1003 ¶430. Specifically, Bublot teaches that to obtain "a dose of 2 ml, one can dilute 0.1 ml of a [stock solution] into 1.9 ml of [**Carbopol™ 974P 2 mg/ml**] ready-to-use solution." Ex.1012 at 16:12-17; Ex.1003 ¶¶430-431. 1.9 ml of a 2 mg/ml Carbopol™ solution will contain 3.8

mg of Carbopol for the 2 mL dose, which is between 500 µg to about 5 mg carbomer per dose. Ex.1003 ¶432. Furthermore, as of December 2004, it was routine in the art of vaccine preparation to determine the optimal amount of a carbomer. Ex.1003 ¶433. Thus, in view of the knowledge of a POSA, it would have been obvious to administer the vaccines of Jestin and/or Blanchard with a carbomer of Bublot in this amount in enhancing the immunogenic effect. Ex.1003 ¶¶429, 434.

5. Claim 10

"The immunogenic composition of claim 1, wherein said composition further comprises a pharmaceutical acceptable salt."

Blanchard discloses 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.1003 ¶436. **PBS** (Phosphate Buffered **Saline**) is a salt solution, specifically a sodium chloride salt solution, in phosphate buffer. Ex.1003 ¶436. If the vaccine is to be administered to a pig, it would be obvious to a POSA to administer a pharmaceutically acceptable salt solution, which has the level of purification necessary for tissue administration. Ex.1003 ¶437.

Furthermore, as of December 2004, it was common to administer vaccines with pharmaceutically acceptable salts; for example, to keep the active ingredients

suspended in water, control the release of active ingredient, keep proteins from sticking to the walls of a container during storage, adjust isotonicity, maintain pH balance, and stimulate the immune system to respond to the vaccine. Ex.1003 ¶¶438-439; *see also* Ex.1007 at 24:27-28 ("Isotonicity can be appropriately adjusted with **sodium chloride and other salts** as needed."). Thus, in view of the knowledge of a POSA, it would be obvious to administer Jestin and/or Blanchard's vaccines with a pharmaceutically acceptable salt. Ex.1003 ¶¶435, 440.

F. GROUND 5: CLAIM 17 IS OBVIOUS UNDER §103(A) OVER BLANCHARD AND/OR JESTIN IN VIEW OF THE KNOWLEDGE OF A POSA, AND ALSO IN VIEW OF HALBUR

To the extent Patent-Owner contends that the three-week limitation of claim 17 is not otherwise taught by the references in Grounds 1-3, that limitation is taught by Halbur and thus claim 17 is obvious in further view of the same.

Halbur describes the successful the vaccination of piglets with a live chimeric PCV1-2 vaccine at three weeks of age. Ex.1003 ¶441. A POSA would have been motivated to combine that teaching from Halbur with Blanchard and/or Jestin because the recombinant ORF2 VLP proteins in Blanchard and Jestin are structurally similar to the PCV1-2 virus in Halbur's vaccine, and vaccination at three weeks of age is both common and advantageous, as explained below. Ex.1003 ¶¶442-443.

Indeed, Blanchard expressly discloses administering a DNA vaccine to piglets at nearly the same age (25 days). *See* Ex.1006 4566; Ex.1003 ¶446.

1. Claim 17

"The method of claim 15, wherein said administration occurs when said pig is about 3 weeks of age."

Halbur discloses that "[p]igs in groups [1, 2 and 3] were vaccinated with the live chimeric [PCV2] vaccine at **3 weeks of age**." Halbur 18; Ex.1003 ¶430. Halbur concludes that the clinical results "indicate that the novel PCV2 chimeric vaccine **is effective** when given to young pigs" with particular maternally derived antibody ("MDA") levels. Ex.1003 ¶¶444-445. In addition, Blanchard's teaching of the administration of an ORF2 DNA vaccines at 25 days of age, which is roughly three weeks of age, renders obvious the administration of an ORF2 protein vaccine at about three weeks of age. Ex.1006 at 4566; Ex.1003 ¶446.

Furthermore, it would be obvious to a POSA to administer such a vaccine at three weeks of age. Ex.1003 ¶447. Today and in 2004, piglets are commonly weaned at around three weeks of age. Ex.1003 ¶448. Furthermore, piglets begin to lose their MDAs, which provide some natural protection against PCV2 infection, at the age of three weeks. Ex.1003 ¶449. "PMWS primarily affects pigs between 5-

18 weeks of age," Ex.1007 at 4:11, thus, there is a limited window of time in which piglets must be vaccinated to prevent PMWS. Ex.1003 ¶450.

Thus, a POSA would have been motivated to administer a single dose of Blanchard and/or Jestin's recombinant ORF2 protein vaccine to piglets three weeks of age as taught by Halbur and as known by a POSA. Ex.1003 ¶451. And in view of the knowledge of a POSA and the results in Halbur, 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 ¶452.

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 24 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 13,880 words, according to the word count tool in Microsoft Word™.

DATED: September 24, 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 '872 Patent:

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