EXHIBIT 3

US005610059A

United States Patent [19]

Joens et al.

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[54] **ETIOLOGICAL AGENT FOR PORCINE ENTERITIS**

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[21] Appl. No.: **973,018**

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[51] **Int. Cl.**[6] **C12N 1/20**; C12N 5/00

[52] **U.S. Cl.** **435/252.1**; 435/822; 435/366

[58] **Field of Search** 435/240.2, 252.1, 435/822; 424/93.3, 93.4, 93.7

[56] **References Cited**

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Attorney, Agent, or Firm—Quarles & Brady

[57] **ABSTRACT**

A novel intracellular organism isolated from enterocytes of pigs affected by Porcine Proliferative Enteritis (PPE) may be cultured by passage in a permissive host cell and may be purified from lysates of such cells. On inoculation, the organism of the present invention causes PPE-like symptoms in pigs. The infectious PPE-causing agent may be used to develop a whole organism bacterin or subunit preparation effective to prevent PPE. In addition, the cultured isolate may be used to prepare a battery of therapeutic and diagnostic monoclonal antibodies directed against the PPE-causing agent. Further, by isolating the genetic material from the agent, various useful fusion proteins may be prepared and the genetic makeup of the organism may be determined.

4 Claims, No Drawings

ETIOLOGICAL AGENT FOR PORCINE ENTERITIS

FIELD OF THE INVENTION

The present invention relates generally to bacterial gastroenteric diseases of pigs and in particular to a bacterial agent which causes porcine proliferative enteritis also known as intestinal adenomatosis.

BACKGROUND OF THE INVENTION

Porcine proliferative enteritis (PPE) is a major problem for the U.S. swine industry. PPE is an intestinal disease of pigs characterized by crypt hyperplasia and by the presence of intracellular campyiobacter-like organisms. Recognition of the disease has increased dramatically in the past ten years, with the incidence ranging as high as 20% and losses estimated at $50 million annually in the U.S. alone. Especially alarming is the apparent increase in incidence among the seed stock industry. The disease has been found worldwide and usually affects post-weanling pigs between six and twenty weeks of age. The clinical response of pigs affected with PPE includes intermittent diarrhea, anorexia, marked dullness and apathy, and a wasting syndrome. Death is not uncommon and is frequently associated with hemorrhage effect on intestines. Four different forms of the disease have been described, but the majority of the literature groups the lesions into two forms, acute and chronic, sometimes referred to as necrotic.

In the acute phase of the disease, macroscopic lesions are characterized by the presence of mesenteric and subacrosal edema and pronounced reticulation of the serosa. The mucosa and muscle layers are thickened, with the mucosa forming deep longitudinal or transverse folds. The ridges of the folds are often hyperemic with some hemorrhage. Ulceration of the mucosa is occasionally evident with areas of viable mucosa adjacent to the lesion. At a microscopic level, acute lesions are characterized by an acute non-specific inflammation accompanied by hyperemia and edema in the lamina propria, by proliferation of epithelial cells, and by hypertrophy of the ileal musculature. The villi and intestinal crypt structure become irregular, with epithelial cell dysplasia. Crypt abscesses form as crypts become branched and fill with inflammatory cells. The villi and lamina propria become swollen due to the presence of edema and inflammatory cells. The submucosa usually contains lymphatic tissue nodules. The muscle of the ileum, especially the circular layers, may become hypertrophied.

In the chronic stage of the disease, macroscopic lesions are characterized by thickening of the lower small intestine. In some cases, inflammation and epithelial necrosis result in the formation of a fibrinous exudate. The mucosa frequently shows hyperemia and hemorrhage with occasional ulceration. The intestine is usually thickened throughout the lower small intestine, but the mucosal thickening is discontinuous, so that the mucosa is always thinner along the mesenteric attachment. Sometimes, the lumen contains a formed blood clot and the colon may contain tarry feces of mixed blood and digesta. The mucosal surface of the affected small intestine may show little gross damage except for the thickening. Erosions, bleeding points, and ulcers are usually not observed. In addition, the regional lymph nodes are markedly swollen. Microscopic lesions in the chronic stage are characterized by a transmural inflammatory reaction. The mucosa is more distorted with long irregular epithelioid projections. Crypts branch, and produce fissures

in the mucosa at the borders of the hyperplastic areas. Ulcers may be seen. Crypt abscesses are also prominent in these areas. Intracellular bacteria, shaped as curved rods, are usually present in the crypt epithelium. The hyperplastic epithelial cells are columnar. Regenerative tissue contains irregularly-formed epithelial cells with a strongly basophilic cytoplasm. Goblet cells are usually infrequent in regeneration areas, but numerous in hyperplastic areas. The lamina propria shows abundant inflammatory cells. Granulomas are occasionally present in ulcerated areas. The submucosa contains dilated lymphatic vessels and fluid-filled tissue spaces. The muscle layers are hypertrophied, with alterations due to the presence of inflammatory cells and fibrin.

The presence of intracellular bacteria in the crypt epithelium of afflicted animals suggests a bacterial etiology for the disease. Although bacteria isolated from such animals are morphologically similar to *Campylobacter spp,* hybridization studies and reproduction experiments using various Campylobacter strains have demonstrated that this organism is not the etiological agent.

Effective PPE control measures have been limited. A basic trial-and-error therapeutic regimen which includes the use of oral and parenteral broad-spectrum antibiotics, antihistamines, corticosteroids, nitroimidazole, and B vitamins, usually becomes quite costly and typically proves ineffective. There has been limited success reproducing PPE using homogenates from affected ileum, and a number of infectious agents have been isolated from PPE-afflicted pigs, though none of these agents has been shown to reproduce the disease after controlled infection. Clearly, the isolation and characterization of the etiological agent of PPE would eliminate some of the trial and error therapeutic practices and would eventually lead to effective control measures using vaccination or medication.

SUMMARY OF THE INVENTION

An intracellular organism isolated from experimentally infected enterocytes produces a PPE-type condition in pigs upon oral inoculation. The isolate may be studied and characterized as to its growth characteristics, surface antigenic properties, and general biology to develop an efficacious vaccine for biological control of PPE.

It is an object of the present invention to provide an easily-manipulated organism capable of repeated passage in vitro and able to cause PPE in a laboratory test animal.

It is another object of the present invention to provide an agent useful for developing prophylactic treatments, including vaccines, against PPE, as well as diagnostic markers for the disease.

Other objects, features and advantages of the invention will become apparent from the following specification.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is directed to the purification of an intracellular bacterial organism which, after exposure to pigs, causes a PPE-like intestinal disease, and is further directed to uses for the organism in developing vaccines and diagnostic reagents useful in the efforts to eradicate PPE from the domesticated pig population.

In this patent application, the bacterial organism of the present invention will be referred to as the PPE-causing agent. The term PPE-causing agent is intended to encompass all such intracellular organisms that may be propagated by

repeated passage in a host cell and that cause macroscopic and microscopic clinical symptoms like those seen in pigs having PPE.

The PPE-causing agent was isolated from infected enterocytes in the intestinal tissue of pigs having PPE lesions. Epithelial cells in the intestinal tissue were detached from the lamina propria by treatment with hyaluronidase. Detached enterocytes were harvested by centrifugation, were resuspended and were treated with antibiotics to kill contaminating gut flora. After washing, the enterocytes were lysed with deoxycholate and were filtered through a 0.65 mm membrane to yield a solution that contained the released PPE-causing agent. The organism has been frozen in liquid nitrogen enterocyte lysates and has been successfully regrown from the frozen cultures by re-inoculation in Henle cells.

To propagate the PPE-causing agent, which appears to be a strict intracellular organism, the filtered lysates containing the PPE-causing agent were used to infect a permissive eukaryotic host, Henle 407, a cell line derived from primary human intestine cells. The infected Henle 407 cells were examined for cytopathic effect (CPE), which was observed 2–4 days after inoculation and was characterized by the elongation and subsequent rounding and sloughing of cells by day 7–10. However, it was possible to sustain the organism by passing 1 ml of supernatant fluid from infected Henle 407 cells onto fresh Henle 407 cells approximately every 7 days.

The infected host Henle 407 cells were used both as a source for obtaining a supply of biologically pure PPE-causing agent and in tests to demonstrate the ability of the PPE-causing agent to induce PPE-like symptoms when inoculated into pigs, which were then observed for clinical signs of PPE. In addition, crude gut homogenates prepared from infected intestinal tissue and normal Henle 407 cells were also administered to piglets as positive and negative controls, respectively.

Results indicated that cells containing the PPE-causing agent were as likely to cause PPE in pigs than homogenates of tissue from infected pigs. Pigs which received uninfected Henle cells were normal at necropsy. In contrast, pigs that received either infected Henle 407 cells or infective gut homogenates exhibited severe diarrhea on day 3 post-inoculation. Three of 4 piglets that received infected Henle 407 cells had gross lesions of PPE at necropsy, as did 5 of 8 piglets that received infective gut homogenates. With one exception, animals having gross lesions also exhibited microscopic lesions. The one exception was a piglet inoculated with uninfected cells which showed mild crypt hyperplasia. Three of 8 piglets that received infective gut homogenates, and 2 of 4 piglets that received infected Henle 407 cells, died due to infection after inoculation.

Transmission electron microscopy (TEM) of negatively stained lysates and scanning electron microscopy (SEM) of fixed lysates made from infected Henle cells revealed high numbers of a slightly curved intracellular organism with approximate dimensions of 0.24–0.27μ×1.4–2.4μ. TEM of thin sections of intestinal tissue from pigs inoculated with infected Henle 407 cells revealed numerous intracellular organisms having similar dimensions. Furthermore, enterocytes from pigs having PPE lesions after inoculation with infected Henle cells appeared totally disarranged or sloughed from the lamina propria.

Having demonstrated the infectivity of the PPE-causing agent, and its ability to induce PPE-like morphological and physiological changes in vivo and in vitro, attention shifts to the envisioned uses for the PPE-causing agent in the arena of PPE prevention and detection. As the PPE-causing agent of the present invention is the first biological isolate able to induce PPE-like disease on inoculation, several envisioned strategies are now made practical which formerly would have been impossible. For example, because the PPE-causing agent may be cultured and purified, it is now possible to develop a bacterin, or inactivated preparation of the PPE-causing agent, using techniques known to the art, which may be administered to pigs at such time during immunological development as to permit the pigs to mount an effective immune response against the agent and against other PPE-causing agents that fall within the scope of the present invention. Bacterins are typically prepared by heat or chemical inactivation of an agent in such manner as to render the agent biologically ineffective, yet antigenically intact.

Alternatively, it is envisioned that various antigenic subunit preparations incorporating proteins from the PPE-causing agent could be prophylactically administered to healthy pigs, which could then mount an immune response against the agent before exposure to a PPE-causing agent. Subunit preparations could be developed in several ways. First, using a classical biochemical approach, purified cell-surface proteins could be prepared from lysates of host cells infected with the PPE-causing agent. The shortcoming of this approach is that it requires exceptionally large quantities of starting material and generates a finite amount of protein from the purified agent.

To produce either a bacterin or a subunit preparation, large-scale cultures of the strict intracellular agent are needed. To determine an optimal host for the agent, other than Henle 407 cells, the agent-containing supernatant from infected Henle 407 cells may be inoculated into a variety of continuous cell line hosts such as, but not limited to, those listed below in Table I.

TABLE I

Source	Example Cell Lines
Mouse	McCoy, L-929
Monkey	VERO-M, BGM
Bovine	EBT, MDBK, EBTh, BFSp
Swine	ST, PK-15
Dog	MDCK
Hamster	BHK-21
Fish	FHM, EPC, TMB, CCO, BB

To monitor the growth of the infectious agent in the potative host cell lines, infected cell lines may be screened by immunofluorescent assay which reveals the presence in host cells of antigenic sites rom the infectious agent. Alternatively, other techniques may be used to monitor the growth of the agent in continuous cell lines. For example, western blots directed against a protein of the agent may be used to compare the relative concentration of the protein in lysates from various hosts.

Alternatively, and preferably, with a purified preparation of the PPE-causing agent in hand, one may exploit a host of recombinant DNA techniques directed toward developing subunit vaccines against the PPE-causing agent. The genetic material of the agent may be easily prepared, by standard methods, from lysates of cell cultures infected with the agent. Genes that encode proteins related to known antigenic proteins, or that encode proteins likely to be antigenic in the PPE-causing agent, may be localized using primers developed from consensus sequences of other eubacterial prokaryotes, and may then be subcloned into fusion-protein

expression vectors of a type generally known to the art. Such vectors may be expressed in heterologous bacterial, animal or plant cell hosts, or expressed in cell-free enzymatic transcription/translation systems. Antigenic fusion proteins encoded by such vectors may be purified and, if properly post-translationally modified, may be used as prophylactic immunogens in piglets.

Genes identified as expressing antigenic proteins may be amplified and purified for subcloning and DNA sequencing using standard techniques known to the art. Isolated genes or gene fragments may, for example, be cloned directly into bacterial plasmid vectors or may first be ligated to linkers having desirable restriction enzyme cut sites. DNA sequencing data obtained from cloned DNA fragments may be compared to known sequences, such as those of the GenBank repository, in an effort to identify the isolated organism and to more precisely explore the molecular biological bases of PPE and its prevention.

The aforementioned bacterin and subunit preparation methods require indicator reagents that identify antigenic proteins or that detect the presence of the PPE-causing agent in host cells. Such indicators may be obtained from polyclonal hyperimmune sera isolated from piglets that have been exposed to PPE or by developing a battery of monoclonal antibodies directed against the intact PPE-causing agent. Monoclonal antibodies against the antigens of the PPE-causing agent may be produced by lysing the infected host cells, purifying the PPE-causing agent from the lysates by gradient centrifugation, purifying the agent's proteins, and separating the proteins using SDS-PAGE electrophoresis. The SDS-PAGE gel may be stained using either Coomassie blue or silver stain to obtain a profile of the organism's proteins and carbohydrates.

To determine which proteins are antigenic in pigs, and, therefore, useful as immunogens, a portion of the SDS-PAGE gel may be subjected to Western blot analysis using sera from pigs convalescent from PPE, or using hyperimmune sera. Transblotted proteins that bind to serum antibodies may be visualized by sequential addition of an appropriate anti-antibody conjugate labelled with peroxidase and a peroxidase-recognizing color substrate. A more precise determination of antigenic reactivity may be determined by subjecting protein fragments, rather than whole proteins, to SDS-PAGE electrophoresis.

A battery of monoclonal antibodies directed against the Western blot-reactive proteins could then be raised by purifying the reactive proteins from the SDS-PAGE gel and injecting them into appropriate laboratory mice strains known to the art. In due course, activated mouse B-cells and an immortalized cell line could be fused and screened to identify hybridomas that produce antibodies directed to the target protein.

To determine which antigenic epitopes are present on the surface of the PPE-causing agent, Henle 407 cells infected with the agent may be harvested, purified by gradient centrifugation, fixed on a microscope slide, and exposed to a battery of monoclonal antibodies raised against the PPE-causing agent. Then, a fluorescein-labeled anti-immunoglobulin is applied to each slide to visualize the cells to which the monoclonal antibody has bound. Monoclonal antibodies directed particularly to surface antigens of the PPE-causing agent could then be grown in quantity and administered prophylactically to pig populations.

Monoclonal or polyclonal antibodies with activity directed against surface antigens of the PPE-causing agent are useful not only as tools for selecting antigenic fusion proteins created in vitro, but also as possible therapeutic reagents in their own right. Presumably, antibodies directed against surface antigenic determinants of the PPE-causing agent, when administered to piglets, would stimulate at least a temporary immune response against PPE.

Furthermore, antibodies developed against the PPE-causing agent may also be used in the field laboratory to monitor pig populations for the presence of the PPE disease using such assays as ELISA assays or Western blots. ELISA assays and Western blots reveal the presence of a marker protein, such as one carried on the surface of a PPE-causing agent, by binding to the protein an antibody that uniquely recognizes the protein. Such an approach would permit the certification of certain stocks as PPE-free, or, when used as part of a routine pig screening program, could alert the grower to a developing problem in a seed stock population.

Alternatively, known antibodies directed against other obligate intracellular organisms and cross-reactive with PPE-causing agent antigens could be used as cross-reactive markers for PPE and might provide a measure of cross-reactive protection against PPE. The degree of antigenic cross-reactivity with other obligate intracellular organisms such as Rickettsia, Ehrlichia or Chlamydia may be determined by an ELISA assay conducted on french press lysates of the PPE-causing agent using existing monoclonal antibodies directed against antigenic determinants on other obligate intracellular organisms. By adding monoclonal antibodies directed against those organisms to bound lysates containing the PPE-causing agent, cross-reacting antibodies protective against PPE may be revealed.

EXAMPLE 1

Isolation of the PPE-Causing Agent

Intestinal tissue from pigs with PPE lesions was longitudinally opened, washed, and sectioned into 5 cm^2 sections. Each section was resuspended into Hank's Balanced Salt Solution (HBSS) and was reacted with N-acetyl cysteine for 60 minutes at 37° C. with constant agitation to remove excess mucus. The mucus-free sections were washed and were resuspended for 1 hour in HBSS containing hyaluronidase to detach epithelial cells from the lamina propria. The sections were then washed and the enterocytes were harvested by centrifugation. The enterocytes were washed and were exposed to gentamicin sulfate and amphotericin B for 24 hours at 4° C. to kill the contaminating gut flora. The treated cells were harvested, washed in HBSS, and lysed with 0.5% deoxycholate for 1 hour at 37° C. with constant agitation to release the intracellular organism. The lysates were passed through a sterile 0.65μ membrane. Filtered lysates were added to confluent monolayers of Henle 407 human intestinal cells in 25 cm^2 flasks (1 ml per flask).

The infected cells were examined for cytopathic effect (CPE) during a 10 day incubation period. CPE was observed in Henle 407 cells 3–4 days after inoculation with enterocyte lysate. The CPE usually consisted of cell elongation, followed by rounding and sloughing of cells between days 7–10.

The intracellular nature of the PPE-causing agent was demonstrated by the inability to culture bacterial or fungal agents from the supernatant fluid on various enriched cell-free media at different atmospheres. Accordingly, the agent was sustained by successive inoculations of 1 ml of supernatant fluid from infected Henle 407 cells onto fresh Henle

407 cell monolayers in 25 cm^2 flasks approximately every 7 days.

EXAMPLE 2

Infectious Nature of the PPE-Causing Agent

The intracellular agent present in enterocyte lysates was propagated in Henle 407 cells to the eighth passage and was then expanded to 20 75 cm^2 flasks. Normal, uninfected Henle 407 cells were also expanded to inoculate control pigs. Sixteen 3-week old conventional piglets were obtained from a farm that had no prior history of PPE. The piglets were fasted for 24 hours and were inoculated with either crude gut homogenates prepared from infective tissue (n=8), infected Henle 407 cells (n=4), or normal, uninfected Henle 407 cells (n=4). On day 0, the piglets were injected with cimetadine to reduce stomach acidity. On days 0, 1, 2, 13, 14 and 15, the piglets were injected with dexamethasone to marginate neutrophils. The piglets were observed daily for 21 days for clinical signs of PPE.

On day 3 post-inoculation, pigs that received infective gut homogenates or infected Henle 407 cells contracted severe diarrhea. Gross lesions of PPE were present at necropsy in 3 of 4 pigs that received infected Henle 407 cells, and in 5 of 8 pigs that received infective gut homogenates. In contrast, pigs that received uninfected Henle 407 cells were normal at necropsy. All pigs exhibiting gross lesions also had microscopic lesions. In addition, a single pig inoculated with uninfected Henle 407 cells exhibited mild crypt hyperplasia. Deaths were recorded in pigs which received infective gut homogenates (3 of 8) or infected Henle 407 cells (2 of 4).

EXAMPLE 3

Characterization of Infectious Agent

Lysates made from Henle 407 cells infected with enterocyte lysates containing the PPE-causing agent were examined by electron microscopy. Transmission electron microscopy (TEM) of negatively stained infected Henle 407 cell lysates and scanning electron microscopy (SEM) of fixed lysates revealed high numbers of a slightly curved bacterium that was 0.24–0.27μ in width and 1.4–2.4μ in length.

After inoculating pigs with infected Henle 407 cells, thin sections of intestinal tissue examined using TEM contained numerous intracellular organisms which were curved and had dimensions of 0.24–0.26μ width and 1.4–2.0μ length. Enterocytes isolated from pigs inoculated with infected Henle 407 cells and having lesions of PPE appeared totally disarranged or sloughed from the lamina propria.

DEPOSIT

A culture of the PPE-causing agent, hosted in Henle 407 cells has been deposited under the terms of the Budapest Treaty with the American Type Culture Collection located at 12301 Parklawn Drive in Rockville, Md. The culture has been accorded Accession No. 55370, and was deposited Nov. 9, 1992 as a cell line designated Ileitis agent IL-A-. All restrictions on access to this deposited specimen will be removed upon issuance of this patent application.

We claim:

1. A biologically pure culture of a mammalian host cell infected by an obligate intracellular bacterium that causes porcine proliferative enteritis after inoculation into pigs having all of the identifying characteristics of ATCC Accession No. 55370.

2. A biologically pure culture as claimed in claim 1 wherein the mammalian host cell is the human intestinal cell line Henle 407.

3. A biologically pure culture as claimed in claim 1 wherein the obligate intracellular bacterium that causes porcine proliferative enteritis is a bacterium having dimensions in the range of 0.24-0.27 micron×1.4–2.4 micron.

4. A biologically pure culture as claimed in claim 1 wherein the obligate intracellular bacterium that causes porcine proliferative enteritis is isolated from enterocytes of a pig having porcine proliferative enteritis.

* * * * *

EXHIBIT 4

Claim Chart comparing U.S. Patent No. 5,610,059 ('059 Patent) to Stills, H.F., *Isolation of an Intracellular Bacterium from Hamsters (Mesocricetus auratus) with Proliferative Ileitis and Reproduction of the Disease with a Pure Culture*, Infection and Immunity, Vol. 59, No. 9, p. 3227-3236 (1991) ("Stills 1991")[1]

'059 Patent Claim 1	Stills 1991 Reference
1. A biologically pure culture of a mammalian host cell infected by an obligate intracellular bacterium	Stills 1991 teaches a biologically pure culture of a mammalian host cell infected by an obligate intracellular bacterium. *See, e.g.,* Stills 1991 at Title, Abstract, 3227, 3229.
that causes porcine proliferative enteritis after inoculation into pigs	Stills 1991 states: "The organism isolated in this study appears to fulfill the criteria to be considered the etiologic agent of hamster proliferative ileitis. The organism was isolated from hamsters with proliferative ileitis and was propagated by utilizing cell culture methodology. The typical lesions of proliferative ileitis were successfully reproduced in hamsters inoculated with the infected cell-free filtrate and the 0.65-μm-pore-size filtrate, while littermates given the uninfected control cell-free filtrate and 0.2-μm-pore-size filtrate remained free of disease. The organism was then reisolated from one of the 0.65-μm-pore-size filtrate-inoculated hamsters which developed proliferative ileitis. The organism was not recovered from hamsters inoculated with uninfected control cell filtrate or the 0.2-μm-pore-size filtrate." Stills 1991 at 3234; *see also, e.g., id.* at Abstract. Stills 1991 further states that "porcine proliferative enteropathy is a disease of pigs with similar lesions and possibly the same etiology as hamster proliferative ileitis." *Id.* at 3227. This limitation would have further been obvious to one of ordinary skill in the art in light of his or her knowledge, the disclosure of Stills 1991 that

[1] Vetmedica applies Stills 1991 in light of Plaintiffs' improper assertions of infringement and improper application of the claims. Vetmedica does not agree with Plaintiffs' application of the claims, or that the claims satisfy 35 U.S.C. § 112. Vetmedica's prior art invalidity contentions also do not represent Vetmedica's agreement or view as to the meaning, definiteness, written description support for, or enablement of any claim contained therein.

	the "porcine proliferative enteropathy is a disease of pigs with similar lesions and possibly the same etiology as hamster proliferative ileitis," *id.* at 3227, and/or the combination of Stills 1991 with Steven McOrist & Gordon H. K. Lawson, *Possible Relationship of Proliferative Enteritis in Pigs and Hamsters*, 15 Vet. Microbiol. 293, Abstract, 299 (1987). One of ordinary skill in the art would have been motivated to combine these references because these references relate to common objectives and subject matter. These references relate generally to proliferative enteritis in pigs and hamsters. Additionally, the references existed and/or were published in the same time period providing further motivation for combination.
having all of the identifying characteristics of ATCC Accession No. 55370.	Plaintiffs do not treat this as a limitation in their infringement contentions. *See* Pls. Resp. to Interrog. No. 1. Accordingly, it should not be treated as a limitation for purposes of invalidity. Regardless, Stills 1991 discloses characteristics of the culture that the applicants allegedly deposited with the ATCC (Accession No. 55370) that are identified in the '059 patent specification and by the applicants in the file history. *Compare, e.g.* Stills 1991 at *Abstract*, 3234, *with* '059 Patent at 1:6–9, 7:38–8:4, '059 File History, 12-19-1994 Amend., at 4–5, *and* '059 File History, 05-31-1994 Amend., at 5, 7.
'059 Patent Claim 2	Stills 1991 Reference
A biologically pure culture as claimed in claim 1 wherein the mammalian host cell is the human intestinal cell line Henle 407.	Stills 1991 discloses that its mammalian host cell line was a Henle 407 cell line. E.g., Stills 1991 at *Abstract* ("The organism was isolated in Intestine 407 . . . cell cultures), 3228 ("Intestine 407 human embryonic intestinal cells . . . were grown"), 3229 ("The organism was readily and continually . . . propagated by infecting confluent Intestine 407 cell cultures with the supernatant from infected cultures"), 3231 ("Examination of infected Intestine 407 cells revealed the presence of bacteria

	morphologically identical to those seen in the ileal cells of infected hamsters").
'059 Patent Claim 3	Stills 1991 Reference
A biologically pure culture as claimed in claim 1 wherein the obligate intracellular bacterium that causes porcine proliferative enteritis is a bacterium having dimensions in the range of 0.24-0.27 micron x 1.4-2.4 micron.	Stills 1991 discloses that its bacterium had dimensions in the range of "0.26 to 0.34 [micron] in width" and "1.4 to 1.7 [micron] in length." *E.g.*, Stills 1991 at *Abstract*, 3231 ("The bacteria in the intestine 407 cells measured 1.4 to 1.7 μm in length by 0.26 to 0.34 μm with a similar trilaminar irregular cell wall.").
'059 Patent Claim 4	Stills 1991 Reference
A biologically pure culture as claimed in claim 1 wherein the obligate intracellular bacterium that causes porcine proliferative enteritis is isolated from enterocytes of a pig having porcine proliferative enteritis.	Stills 1991 discloses that its bacterium causes proliferative enteritis after inoculation in hamsters, *e.g.*, Stills 1991 at *Abstract*, 3234 ("The immunohistochemistry studies using a specific polyclonal antibody confirm that the curved organisms seen in the epithelial cells of the hamsters with experimentally induced proliferative ileitis are the same that were present in the cell culture further supporting the role of this organism in the disease pathogenesis."), and that "porcine proliferative enteropathy" and hamster proliferative enteritis possibly had the "same etiology," *id.* at 3227. This limitation would have further been obvious to one of ordinary skill in the art in light of his or her knowledge, the disclosure of Stills 1991 that the "porcine proliferative enteropathy is a disease of pigs with similar lesions and possibly the same etiology as hamster proliferative ileitis," *id.* at 3227, and/or the combination of Stills 1991 with Steven McOrist & Gordon H. K. Lawson, *Possible Relationship of Proliferative Enteritis in Pigs and Hamsters*, 15 Vet. Microbiol. 293, Abstract, 299 (1987). One of ordinary skill in the art would have been motivated to combine these references because these references relate to common objectives and subject matter. These references relate generally to proliferative enteritis in pigs and hamsters. Additionally, the references existed and/or were published in the same time period providing further motivation for combination.

EXHIBIT 5

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 6

Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/973,018	11/09/92	JOENS	L 92-214-9006-

EXAMINER

HUNG, D

ART UNIT	PAPER NUMBER
1808	5

DATE MAILED: 04/07/93

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18M1

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/19/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application.
   Of the above, claims 11-14 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-10 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 11-14 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Claims 1-14 are presented for examination.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-10, drawn to a culture, classified in Class 435, subclass 240.2.

II. Claims 11-12, drawn to an antibody treatment, classified in Class 424, subclass 85.8.

III. Claims 11 and 13, drawn to a vaccine, classified in Class 424, subclass 88.

IV. Claim 14, drawn to a fusion protein, classified in Class 425, subclass 68.1.

Group I, Group II, Group III and Group IV are mutually exclusive and patentably distinct products. They have acquired a separate status in the art as a separate subject for inventive effect and require independent searches (as indicated by the different classification). The search for each of the above inventions is not so-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one Group would not necessarily anticipate or make obvious another Group. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper.

During a telephone conversation with Nicolaus Seay on March 25, 1993 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10. Affirmation of

this election must be made by applicant in responding to this Office action. Claims 11-14 withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Since the cell line is essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the cell line is not so obtainable or available, the requirements of 35 USC § 112, first paragraph may be satisfied by a deposit of the cell line. The specification does not disclose a repeatable process to obtain the cell line and it is not apparent if the

cell line is readily available to the public. The specification must contain the date that the cell line was deposited, the name of the cell line and the address of where the cell line was deposited. It is noted that the applicant(s) have deposited the organism but there is no indication in the specification as to public availability.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) the deposit will be replaced if it should ever become inviable.

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 are indefinite in their recitation of "PPE-like" or "PPE-causing" and "agent". It is suggested that PPE be written out in its full form for clarity. The phrase "PPE-like" is vague in not defining the characteristics of porcine proliferative enteritis. It is also confusing in the fact that the phrase "PPE-like" would imply that the agent does not actually cause PPE in the following dependent claims the phrase "PPE-causing" is found. The term "agent" is not adequately defined and could be interpreted to mean any number compositions or materials.

Claim 1 is indefinite in its recitation of "host cell". The phrase "host cell" is not adequately defined and it is unclear what would constitute a host cell.

Claim 3 is indefinite in its recitation of "organism". The term organism is too broad as it encompasses fungi, bacteria, yeast as well as plants and animals.

Claims 5 is indefinite in its recitation of "having the characteristics of ATCC Accession No.". It is unclear what

characteristics are being claimed.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Lomax et al. (A).

The claimed invention is drawn to a preparation of a host cell and a PPE-causing agent.

Lomax et al teaches that porcine proliferative enteritis is associated with the intracellular presence of Campylobacter sp-like organisms (page 1622, first column). The reference teaches that the organisms are .2 -.3 um x 2-3 um (page 1622, second column). Note that the size of the claimed invention overlap with the reference's size range. Lomax et al teach that the organism is found within the intestinal mucosa of pig (page 1622, second column). Although the reference does not infect host cells with the organism, it would be obvious to one of ordinary skill in the art to do so in order to study the disease in vitro. The choice of using a host cell that is an intestinal cell line would have

been obvious given the fact that Lomax et al teach the organism was originally isolated from the intestines of pigs.

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah L. Hung whose telephone number is (703) 308-0665.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

D L Hung
D.L. Hung

March 31, 1993

DAVID M. HAFF
PRIMARY EXAMINER
ART UNIT 1808

EXHIBIT 7

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/973,018	11/09/92	JOENS	92-214-9006-

EXAMINER	
LARSON, K	
ART UNIT	PAPER NUMBER
1806	14

18N2/0310

NICHOLAS J. SEAY
QUARLES & BRADY
P.O. BOX 2113
MADISON, WI 53701-2113

DATE MAILED: 03/10/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/28/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-5, 11-14 are pending in the application.
   Of the above, claims 11-14 are withdrawn from consideration.
2. ☒ Claims 6-10 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-5 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Claims 1-5 are presented for examination.

Claims 6-10 have been canceled.

Claims 11-14 have been withdrawn from consideration.

The Amendment filed December 22, 1994 has been received and entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the claimed invention.

Specifically, an adequate written description is lacking for the microorganism with regard to the specific species and strain used. There is no indication regarding morphological and physiological features of the microorganism except size. Thus the skilled artisan would not know when the agent had been obtained. In view of the insufficient description, the disclosure is deemed to lack sufficient guidelines to permit those skilled in the art to practice the invention without excessive experimentation.

2. Claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

3. Claims 1-4 rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a biologically pure culture of Henle 407 cells hosting a causative

agent of porcine proliferative enteritis deposited under ATCC Accession No. 55370. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicant's claims are broadly directed to a biologically pure culture of any mammalian host cell line containing any causative agent of porcine proliferative enteritis. The specification only demonstrates the ability of the Henle 407 cell line to host the specific causative agent discussed since the agent is a strict intracellular organism.

The single agent/host combination presented, i.e., Henle 407 cells hosting the causative agent, does not delineate a set of examples for any and all causative agents contained in any and all host cells lines. It is noted that applicant has recited a number of cell lines on page 7 of the specification. However, mere recitation is insufficient. One would still have to determine if the cell lines were optimal hosts and based on the lack of information in the specification regarding the agent, this would cause undue experimentation. Thus, to practice applicant's invention as broadly claimed would require undue experimentation by the skilled artisan.

4. Claims 1-4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is rendered vague and indefinite by claiming that one may obtain the causative agent of porcine proliferative

enteritis from pigs which just exhibit symptoms of the disease. It is not clear how the agent can be obtained from pigs which do not necessarily have PPE.

5. Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Alderton et al. (R1) for reasons of record as set forth at pages 4 and 5 of the Office action of August 18, 1994. Applicant's arguments have been carefully considered, but are not deemed to be persuasive of error in the rejection.

Applicant has argued that the agent of Alderton is a *Campylobacter* agent unlike the claimed agent. In addition, applicant notes that the agent of Alderton can grow *in vitro* whereas the claimed agent is a strict intracellular organism.

The differences between the agent of Alderton and that claimed have been noted. However, the teachings of Alderton suggest how one may locate PPE-causing agents and the teachings of the specification are insufficient to verify that the claimed agent is not at least closely related to the agent discussed in Alderton. Therefore, it would have been obvious to obtain the claimed agent in view of the fact that such agents are known and Alderton teaches how they may be discovered.

The reference is deemed to disclose all essential elements of the claimed invention. Applicant's arguments have failed to establish that the *prima facie* case of obviousness established by the cited references has been overcome.

6. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R, § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kristin Larson whose telephone number is (703) 305-7811. The Group 1800 receptionist may be reached at (703) 308-0196.

KL

Kristin K. Larson
March 9, 1995

JOHN W. ROLLINS
PRIMARY EXAMINER
ART UNIT 1801

EXHIBIT 8

PATENT

#7/8
11/16/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Joens & Glock
Serial No.: 07/973,018
Filing Date: November 9, 1992
For: ETIOLOGICAL AGENT FOR PORCINE ENTERITIS

Date: October 7, 1993
Docket No.: 9221490069
Group Art Unit : 1808

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231 on the date indicated below.

Nicholas J. Seay
(Name of applicant, assignee or registered representative)

(Signature)

October 7, 1993

AMENDMENT

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated April 7, 1993 in the file of the above-identified patent application, please amend that application as follows.

In the Specification:

Page 13 line 18, delete "_____" and insert therefore -55370, and was deposited Nov. 9, 1992 as a cell line designated Ileitis agent IL-A--.

In the Claims:

Please amend claims 1, 13, and 15 as follows:

1. (Amended) A biologically pure culture of a mammalian host cell containing an intracellular bacterium [agent] that causes [PPE-like] symptoms of porcine proliferative enteritis after inoculation into pigs.

3. (Amended) A biologically pure culture as claimed in claim 1 wherein the intracellular [PPE-causing agent] bacterium causing symptoms of porcine proliferative enteritis is [an organism] a bacterium having dimensions in the range of 0.24-0.27 μ x 1.4-2.4 μ.

5. (Amended) A biologically pure culture of a mammalian host cell and [a PPE-causing agent] a bacterium that causes symptoms of porcine proliferative enteritis in inoculated pigs, the bacterium having the characteristics of ATCC Accession No. [_____] 55370.

Remarks

By an Office Action dated April 7, 1993 in the file of the above-identified patent application, the Examiner in charge of the application has imposed a requirement for restriction and has rejected the application upon various grounds both of claim language and prior art. In response to that rejection, the applicant has amended the claims and responded herewith. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

The first issue raised in the Office Action is the requirement for restriction, which the Examiner imposed between claims directed to the etiological agent itself and claims directed to antigens, vaccines or fusion proteins made from that agent. First, the applicants wish to confirm the election of the Group I claims, directed to a culture of the etiological agent, with traverse.

With regard to the propriety of the requirement for restriction, the applicants wish the Examiner to reconsider this requirement. The claims in Groups II, II, and IV are all inextricably linked to the subject matter of the agent claimed in Group I. Note, in particular, that claim 11 was intended to claim a therapeutic preparation made from a culture of the organism of claim 1, e.g. a vaccine made using the culture. Since the vaccine would be made from the culture, it would seem that the two sets of claims are highly inter-related, would involve the same search and art, and that the issues raised in the consideration of either set of claims would inherently involve the same issues as would be considered for the other set of claims. As such, it would seem most efficient for all concerned if the claims could all be considered in a common patent application, and it is therefore requested that this requirement for restriction be reconsidered.

Neither the election of Group I, nor the possible removal from consideration of the other claims, changes the designation of inventorship of the application.

The Examiner next rejected the application for lack of enablement, due to lack of showing regarding the deposit. The applicants have, in fact, made a deposit under the terms of the Budapest Treaty with the ATCC. The date of deposit and nomenclature used for the deposit have been added to the specification, as requested. The deposit was made November 9, 1992, and was accorded accession No. 55370. The undersigned, registered to practice before the U.S. Patent and Trademark Office, hereby states that the strain will be irrevocably and without restriction released to the public upon the issuance of this patent application as a patent. It is believed that the above statement should overcome this grounds of rejection.

All the claims of the application were rejected due to indefiniteness under 35 USC §112. By changes to the claims above, the applicants have attempted to cure each identified informality. The terms "PPE" has been spelled out and the term "agent" has been replaced by "bacterium." The term "host cell" has been modified to recite that it is mammalian, so as to place a limitation on the type of host cell. Note that since the etiological agent is an obligatory intracellular organism, a susceptible host cell is

required to maintain the organism alive, and it is for that reason that the host cell has been included in the claimed combination. It is hoped that these changes satisfy the Examiner's requirements for definiteness.

On page 6 of the Office Action, a rejection on prior art is made over a reference to Lomax et al. Lomax et al. describe research directed toward the isolation of the causative agent of porcine proliferative enteritis which resulted in the isolation of a putative causative agent, a strain of Campylobacter sputorum subsp. mucosalis. Note, however, that even in the text of the Lomax paper, all that is stated is that the agent was "associated" with the disease, rather than clearly being the causative agent.

The applicants of this application submitted an Information Disclosure Statement for this application which was received by the Patent and Trademark Office on March 19, 1993, but which apparently had not made its way to the Examiner before the Office Action was issued. With that submission, which by now should be in the file for this application, is a chapter on bacterial diseases, by Rowland and Lawson, from a book on swine diseases. In that chapter, on page 547, Rowland and Lawson comment on the studies that suggested that Campylobacter strain have been associated with porcine enteritis, but are forced to conclude, on page 548, that "One cannot at present consider either [Campylobacter] mucosalis or hyointestinalis to be solely responsible for the changes of PIA." In other words, the authors reported that the Campylobacter strains occupy infected tissues, but are not the causative agent for the disease, since they alone cannot cause the disease.

In contrast, the agent of the present invention, previously unknown, is quite capable of causing pathogenic enteritis in swine without other agents being present. See, e.g. Example 2 of the present specification. The inventors here, one of whom incidentally was a co-author of the Lomax et al. paper, have now demonstrably found the causative agent. Thus, not only is it true that Lomax does not describe the true causative agent, the applicant here does, and the agent is much different from the Campylobacter described by Lomax. The agent here, an obligatory

intracellular bacterium, cannot be confused with the bacterium of Lomax, which can clearly be grown extrinsic to any host (see Lomax page 1623, second full paragraph).

Thus, the bacterial disease agent described and claimed in the present patent application is neither the same as described by Lomax nor is it obvious in view of the teachings of Lomax. The organism of Lomax is not truly responsible for the disease, although it is opportunistically associated with it. The novel organism described and claimed here is the true etiological agent, and it is also clearly not the organism described by Lomax. Accordingly, a culture of the agent disclosed and claimed here is in no way either anticipated or obvious over the teachings of Lomax.

Wherefore, the Examiner is again invited to review the merits of this patent application. A separate petition for extension of time is submitted herewith so that this amendment will be considered as timely filed. An early and favorable reply is solicited.

Respectfully submitted,

Nicholas J. Seay, Reg. No. 27,386
Attorney for Applicant
Quarles & Brady
P.O. Box 2113
First Wisconsin Plaza
Madison, Wi 53701
(608) 251-5000

EXHIBIT 9

MAIL ROOM AUG 14 1995 PAT. & TRADEMARK OFF.

1800

AF GP 1808
#16/E
8/23/95

I hereby certify that this correspondence is being deposited with the United States Postal Service on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Date of Signature and Deposit: August 10, 1995

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Lynn A. Joens
Robert D. Glock

Date: August 10, 1995

Serial No.: 07/973,018

Group Art Unit: 1808

Filed: November 9, 1992

File No.: 92-214-9006-9

For: ETIOLOGICAL AGENT FOR PORCINE ENTERITIS

Examiner: K. Larson

AMENDMENT

Assistant Commissioner for Patents
Box AF
Washington DC 20231

Dear Sir:

In response to an Office Action mailed March 10, 1995 in connection with the above-identified application, please amend the application as follows:

In the Claims:

Please amend Claim 4 as follows:

4. (Amended Three Times) A biologically pure culture as claimed in claim 1 wherein the obligate intracellular bacterium that causes porcine proliferative enteritis is isolated from

E1

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enterocytes of a pig having [the symptoms of] porcine proliferative enteritis.

E1

REMARKS

In an Office Action mailed March 10, 1995, the Examiner in charge of the above-identified patent application objected to the specification under 35 U.S.C. §112, first paragraph, and rejected the claims as being unsupported by an adequate written description. The Examiner rejected Claims 1-4 under Section 112, first paragraph asserting overbreadth in both the host cell and bacterium recited. Claims 1-4 were rejected under Section 112, second paragraph for indefiniteness. Claims 1-5 are rejected under 35 U.S.C. §103 as being unpatentable over Alderton et al.

In view of the preceding amendment to the claims and the arguments presented herein, the applicants respectfully request reconsideration of the merits of this patent application.

Pursuant to the transitional provisions of 37 C.F.R. §1.129(a), removal of the final rejection in this case is requested. Under these provisions, payment of the fee specified in 37 C.F.R. §1.17(r), believed to be $730.00 for an applicant other than a small entity, results in removal of the final rejection and consideration by the Examiner of an additional submission by the applicants. Authority is hereby given to charge the fee for removal of the final rejection to Deposit Account No. 17-0055. Please charge any underpayment or credit

any overpayment to this same deposit account. A duplicate copy of this response is filed herewith to facilitate this charge.

The Examiner asserts that the specification fails to provide an adequate written description of the claimed invention because it does not specify the particular species and strain of microorganism isolated by the inventors. The applicants respectfully disagree with the Examiner's contention. The applicants have done all that was possible, and certainly, all that was required, to describe the organism that is the subject matter of the instant application. In at least three ways, one of ordinary skill can readily determine whether he or she is in possession of the subject organism. First, the size characteristics of the organism provide an initial screen to determine whether it is likely or unlikely that the organism is that recited in the claims. Second, a skilled artisan can readily distinguish porcine proliferative enteritis from other disorders using the guidance recited in the specification and the clinical diagnostic tools available to those of ordinary skill in the art. Finally, and perhaps most importantly, if an organism meets both the size and clinical tests, one of ordinary skill, using extremely routine culture methods, can readily determine whether the organism is an obligate intracellular bacterium or another organism capable of independent reproduction in the absence of a host cell.

These analyses are precisely those used by persons of ordinary skill in the art to catalogue individual microorganisms,

particularly previously unknown organisms. Thus, it is neither surprising, nor improper, that the applicants had not assigned a species and strain name to the organism. What they did instead, as any skilled microbiologist would have done, is to identify the characteristics that distinguish the organism from those known to the art. Such a step is an important precursor to taxonomic designation.

The Examiner has pointed to no organism having the recited characteristics, other than that described by the inventors. In the absence of such an organism, it is believed that the description provided by the inventors is certainly adequate to support the pending claims. These rejections for lack of an adequate written description should be withdrawn.

The Examiner has also rejected Claims 1-4, suggesting that the disclosure enables only claims limited to the specific culture of Henle 407 cells hosting a causative agent of porcine proliferative enteritis. The applicants respectfully maintain that the Examiner is imposing too strict a requirement upon the identity of the host cell. The situation is analogous to that of a claim reciting a genetic element, such as a plasmid, hosted in a bacterial cell capable of supporting replication of the element. Claims are routinely obtained to such bacterial cultures, yet, it has not been the experience of the undersigned that the identity of the bacterial host cell need be specified in the broadest claim. In the absence of such a host cell, the genetic element would be incapable of reproduction. The host

cell acts merely as a holder or carrier that maintains the genetic element in successive generations.

Likewise, here, the applicants have characterized an obligate intracellular bacterium that causes porcine proliferative enteritis. Such an organism cannot reproduce outside of the holder or carrier host cell. The source and characteristics of the host cell, apart from its ability to sustain the bacterium, are simply unimportant. In much the same way that the Office neither requires species nor strain designation for a bacterium that hosts a genetic element, the applicants believe it improper to require the claims to be limited to either the particular cell line used as a host or to the particular ATCC deposit of the organism in the host.

For the reasons discussed above, the applicants further believe that their claims need not be limited to the particular organism resident in ATCC Accession No. 55370. To reiterate, the applicants have described sufficient information about the organism to distinguish it from any others previously known and to permit one to ascertain with reasonable certainty whether they are in possession of an organism that meets the requirements of the claim. Therefore, these rejections should be reconsidered and withdrawn.

The Examiner next rejected Claims 1-4 under Section 112, second paragraph for indefiniteness. The Examiner only commented on Claim 4 and provided no basis for the rejection for indefiniteness of Claims 1-3. With regard to Claim 4, the

applicants have amended the claim to delete the phrase "the symptoms of" so that the claim now recites that the bacterium is isolated from enterocytes of a pig having porcine proliferative enteritis. Thus, it is believed that this rejection is overcome and should be withdrawn.

Finally, the claims are rejected under Section 103 as being unpatentable over Alderton et al. The applicants have previously noted the distinctions between the Campylobacter-like bacterium of Alderton and the bacterium of the present invention. Reference is once again made to the remarks dated December 19, 1994 in response to a prior office action, and those remarks are incorporated herein. In addition, the applicants wish to stress that although Alderton demonstrated certain symptoms of PPE, namely gross pathological lesions, ileitis, etc., it is not apparent from Alderton that proliferative porcine enteritis was induced. There is no indication in Alderton that the organism used was responsible alone for true porcine proliferative enteritis. While an organism may cause certain symptoms of the disease, it may not be sufficient to cause the disease itself, as the Examiner has already noted. True PPE has been shown by the applicants and, subsequently, by others, to be caused by an obligate intracellular bacterium which is demonstratably different from that of Alderton most notably in its intracellular nature.

Once again, the applicants dispute the assertion that the specification is insufficient to verify that the claimed agent is

not at least closely related to the agent discussed in Alderton. The claimed agent is an obligate intracellular organism. The organism of Alderton is not. Subsequent research by those skilled in the art supports the contention of the applicants that the causative agent of PPE is an obligate intracellular organism (see McOrist et al., "The Etiology of Porcine Proliferative Enteropathy (Ileitis)," Conference of Research Workers in Animal Diseases, November 8 and 9, 1993 (Abstract), already of record. The report of McOrist appeared a year and one-half after the Alderton paper became available. There is certainly no indication in McOrist of any uncertainty with regard to the actual causative agent of PPE. McOrist could not have been more clear in stating that "the etiology of proliferative enteropathy is clearly the obligate intracellular bacteria" which he named ileal symbiont "Ileobacter intracellularis." McOrist concluded the abstract noting that "some gut flora is apparently required to optimize conditions for growth of the causative agent in vivo." The non-intracellular organism of Alderton may very well be one of such gut flora. However, it is certainly the conclusion in the art that the causative agent is an obligate intracellular bacterium. That is not what Alderton isolated and it is incorrect to assert that possession of an agent that is clearly not the causative agent in any way would facilitate isolation of the causative agent.

In the absence of additional work, one might have been led to believe that the Alderton organism was, in fact, the causative

agent of PPE. However, for whatever reason, the art was not satisfied that the causative agent had truly been uncovered. The subsequent realization by the present inventors and, then, others, was that all of the symptoms of PPE could only be induced by an obligate intracellular organism. It would only have been by the application of hindsight that one would know that the causative agent could be isolated in a manner similar to that used by Alderton. Upon recognizing that Alderton did not have true causative agent, one might then have suspected a pair of biological agents or even a requirement for a non-infectious component. It so happened that the causative agent was, in fact, a bacterium, but the properties and nature of that organism, especially its obligate intracellular lifestyle, could not have been predicted, even from Alderton. The Examiner has pointed to no factual basis for presuming any relationship between the Alderton bacterium and that of the present inventors. The suggestion that the Alderton organism is somehow closely related to the inventors' organism but is of a different species, grows on different media, and has different host cell requirements, is not realistic. Other than challenging the inventors to demonstrate that the two are not closely related, the Examiner has offered no basis for a suggestion that the organisms are related in any way other than by both being bacteria. As the applicants have previously noted, their organism is not a Campylobacter and cannot grow outside of a host cell. Accordingly, the applicants respectfully request the Examiner

revisit this issue and, if the rejection is maintained, to provide a more concrete basis for alleging the similarity of the Alderton organism to that of the present inventors.

Having responded to each and every ground of rejection, and having removed the final rejection pursuant to the transitional provisions of the new patent rules, the applicants respectfully request reconsideration of the merits of this patent application.

A separate petition for extension of time for two months is submitted herewith so that this response will be considered as timely filed.

Respectfully submitted,

Nicholas J. Seay, Reg. No. 27386
Attorney for Applicants
QUARLES & BRADY
P.O. Box 2113
Madison, WI 53701-2113

(608) 251-5000

QBMAD1\82004

EXHIBIT 10

Notice of Allowability	Application No. 07/973,018	Applicant(s) Lynn A. Joens et al.
	Examiner Kristin K. Larson	Group Art Unit 1808

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowence and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *the Amendment filed May 28, 1996*

☒ The allowed claim(s) is/are *1-4*

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____ .

☐ including changes required by the proposed drawing correction filed on _____ , which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 180

PROPOSED EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C R 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the vment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Nicholas Seay on August 25, 1996.

2. The application has been amended as follows:

- In the claims:

  - in claim 1, line 2, the phrase "containing ~~an~~" has been changed to the phrase --infected by--.

  - in claim 1, line 4, the phrase "of the culture" has been deleted.

  - in claim 1, line 4, the phrase --having all of the identifying characteristics of ATCC Accession No. 55370-- has been inserted after the term "pigs."

  - in claim 3, lines 4 and 5, the term "u" has been changed to the term --micron--.

  - claims 5 and 11-14 have been canceled.

3. The following is an examiner's statement of reasons for allowance: the closest prior art does not teach or suggest the isolation of a microorganism in a mammalian host cell line wherein the microorganism causes porcine proliferative enteritis (PPE). The claimed PPE-causative agent is an

obligate, intracellular microorganism. The microorganism taught by the closest prior art causes only symptoms of PPE and is not an intracellular organism.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kristin Larson, whose telephone number is 703-305-7811. The fax number for Art Unit 1808 is 703-305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is 703-308-0196.

Kristin K. Larson
August 25, 1996

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 182

EXHIBIT 11

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 12

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 13

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 14

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 15

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 16

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Etiological Agent for Porcine Enteritis,
the specification of which (check one) ☐ is attached hereto. ☒ was filed on 11/9/92 as Application No. 07/973,018 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations § 1.56(a). In this regard, I hereby state that I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the same has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than six months (for a design patent application) or more than twelve months (for a utility patent application) prior to this application.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
N/A			☐	☐
(Number)	(Country)	(Day/month/year filed)		
			☐	☐
(Number)	(Country)	(Day/month/year filed)		

4 I hereby appoint the following practitioner(s) to prosecute this application and all continuation and divisional applications based thereon, and to transact all business in the Patent and Trademark Office connected therewith: Thad Kryshak 19428, Carl Schwartz 29437, Nicholas J. Seay 27386 and Jean C. Baker 35433

Direct all telephone calls to Nicholas J. Seay at telephone no. 608/251-5000 Address all correspondence to: Nicholas J. Seay, c/o Quarles & Brady, P.O. Box 2113, Madison, WI 53701-2113

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
1-00 Lynn A. Joens	Lynn A Joens	1/4/93
RESIDENCE 11421 Placita Madre, Tucson AZ 85749		CITIZENSHIP U.S.
POST OFFICE ADDRESS same of AZ		
FULL NAME OF SECOND JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
2-00 Robert D. Glock	Robert D Glock	1-10-93
RESIDENCE 1031 Mirrormere Cir, Fort Collins CO 80526		CITIZENSHIP US
POST OFFICE ADDRESS Same		
FULL NAME OF THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		

EXHIBIT 17

In The Matter Of:

Intervet, Inc.

vs.

Boehringer Ingelheim Vetmedica, Inc.

Nicholas Seay

August 1, 2012

MERRILL CORPORATION

LegaLink, Inc.

311 South Wacker Drive
Suite 300
Chicago, IL 60606
Phone: 312.386.2000
Fax: 312.386.2275

15:41:43 of Dr. Joens and Dr. Glock in connection with the
15:41:46 '059 patent. Is that correct?
15:41:49 A. I assume so.
15:41:51 Q. Can you take a look at the page ending
15:41:53 in 040 of Exhibit 11?
15:42:02 A. Okay. I see that.
15:42:07 Q. Is this declaration of Dr. Joens and
15:42:09 Dr. Glock that you submitted in connection with
15:42:11 the '059 patent?
15:42:15 A. It looks to be. Yes.
15:42:18 Q. And you submitted this to the PTO.
15:42:20 Correct?
15:42:21 A. I believe I did.
15:42:23 Q. And Dr. Joens and Dr. Glock are
15:42:26 acknowledging their duty to disclose information
15:42:29 to the PTO in this declaration. Correct?
15:42:32 A. They signed a document which read, "I
15:42:35 acknowledge the duty to disclose information which
15:42:37 is material to the examination of the application,
15:42:40 in accordance with Title 37 CFR, Section 156A."
15:42:45 That's the old rule 156, which dealt
15:42:49 with duty to disclosure.
15:42:54 Q. Had you any reason to doubt that the
15:42:56 inventors did not understood their duty of
15:42:58 disclosure, would you have submitted this

5068673c-6897-4df4-a596-6763aa6e663b

15:43:01 declaration to the PTO?

15:43:04 A. I thought he was going to object, so

15:43:05 I'll have to hear again. Excuse me.

15:43:05 (The reporter read the record as

15:43:05 requested.)

15:43:05 THE WITNESS: Read that again.

15:43:05 (The reporter read the record as

15:43:05 requested.)

15:43:33 BY MS. HOLLIS:

15:43:33 Q. I'll restate the question, because I

15:43:36 don't know if it's transcribed correctly.

15:43:37 A. Okay.

15:43:39 Q. Had you any reason to doubt that

15:43:41 Dr. Joens or Dr. Glock understood their duty of

15:43:45 disclosure, would you have submitted this

15:43:47 declaration to the PTO?

15:43:52 A. If I believed they did not -- the

15:43:54 answer is no.

15:44:03 Q. Do you have any reason to believe that

15:44:05 they did not understand their duty of disclosure?

15:44:11 A. No.

15:44:15 Q. Do you have any reason to believe that

15:44:16 you did not inform the inventors of their duty of

15:44:19 disclosure?

15:44:21 A. No.

5068673c-6897-4df4-a596-6763aa6e663b

EXHIBIT 18

Miller, Jennifer A.

From: Graham, Mary [MGraham@MNAT.com]
Sent: Tuesday, August 07, 2012 8:11 PM
To: Hollis, Amanda
Cc: 'Greg Bonifield'; 'Ray Nimrod (raynimrod@quinnemanuel.com)'; 'Aaron Kaufman'; Santhanam, Hari; rhorwitz@Potteranderson.com; dmoore@Potteranderson.com1; Hales, Bryan S.; Pals, Mark A.; Desh, George; Fahnestock, Derek
Subject: RE: Intervet v. Vetmedica

Amanda,
Your email of this evening below requesting Plaintiffs' position on Vetmedica's "request to amend its answer and counterclaims to assert that the '059 patent is unenforceable as a result of inequitable conduct" did not attach the proposed amendment which you propose to file or otherwise set forth the basis for a claim of unenforceability. Your email also did not explain the basis for why any such amended pleading would be appropriate 5 ½ months after the agreed-upon date set forth in the scheduling order for amendment of pleadings. Please provide this information and Vetmedica's proposed pleading so that we can have the information necessary to consider your request.
Regards,
Mary

From: Hollis, Amanda [mailto:ahollis@kirkland.com]
Sent: Tuesday, August 07, 2012 7:24 PM
To: Greg Bonifield
Cc: Graham, Mary; Ray Nimrod (raynimrod@quinnemanuel.com); Aaron Kaufman; Santhanam, Hari; Horwitz, Richard; Moore, David; Hales, Bryan S.; Pals, Mark A.; Desh, George
Subject: Intervet v. Vetmedica

Greg,

Vetmedica intends to request leave to amend its answer and counterclaims to assert that the '059 patent is unenforceable as a result of inequitable conduct. Please let us know if Plaintiffs will oppose Vetmedica's request.

Regards,

Amanda

Amanda Hollis | Kirkland & Ellis LLP
300 North LaSalle | Chicago, IL 60654
312-862-2011 | amanda.hollis@kirkland.com

****
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To ensure compliance with requirements imposed by the U.S. Internal Revenue Service, we inform you that any tax advice contained in this communication (including any attachments) was not intended or written to be used, and cannot be used, by any taxpayer for the purpose of (1) avoiding tax-related penalties under the U.S. Internal Revenue Code or (2) promoting, marketing or recommending to another party any tax-related matters addressed herein.

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EXHIBIT 19

Miller, Jennifer A.

From: Greg Bonifield [gregbonifield@quinnemanuel.com]
Sent: Wednesday, August 22, 2012 8:29 PM
To: Hollis, Amanda; Graham, Mary
Cc: Hales, Bryan S.; Santhanam, Hari; dmoore@Potteranderson.com1; rhorwitz@Potteranderson.com; Pals, Mark A.; Ray Nimrod; Aaron Kaufman; Desh, George
Subject: RE: Proposed pleading

Amanda,

Vetmedica's proposed amendment is tardy and Vetmedica has not provided support as to how it would establish the right to amend in consideration of the pertinent factors for amending, often stated as undue delay, bad faith, dilatory motive, prejudice, and futility.

Regards,
Greg

From: Hollis, Amanda [ahollis@kirkland.com]
Sent: Wednesday, August 22, 2012 12:09 AM
To: Greg Bonifield; Graham, Mary
Cc: Hales, Bryan S.; Santhanam, Hari; dmoore@Potteranderson.com1; rhorwitz@Potteranderson.com; Pals, Mark A.; Ray Nimrod; Aaron Kaufman; Desh, George
Subject: RE: Proposed pleading

Greg,

What "applicable requirements" do you believe our pleading does not meet and why?

Amanda

From: Greg Bonifield [mailto:gregbonifield@quinnemanuel.com]
Sent: Tuesday, August 21, 2012 2:16 PM
To: Hollis, Amanda; Graham, Mary
Cc: Hales, Bryan S.; Santhanam, Hari; dmoore@Potteranderson.com1; rhorwitz@Potteranderson.com; Pals, Mark A.; Ray Nimrod; Aaron Kaufman; Desh, George
Subject: RE: Proposed pleading

Amanda,

Vetmedica's tardily-proposed amended answer does not appear to meet the applicable requirements. Plaintiffs do not agree to its filing.

Regards,
Greg

From: Hollis, Amanda [mailto:ahollis@kirkland.com]
Sent: Monday, August 20, 2012 10:13 AM
To: Greg Bonifield; Graham, Mary
Cc: Hales, Bryan S.; Santhanam, Hari; dmoore@Potteranderson.com1; rhorwitz@Potteranderson.com; Pals, Mark A.; Ray Nimrod; Aaron Kaufman; Desh, George
Subject: FW: Proposed pleading

Greg and Mary,

We have not heard back from you on this. Please let us know by tomorrow if you will not oppose our proposed amendment.

Regards,
Amanda

From: Hollis, Amanda
Sent: Tuesday, August 14, 2012 5:37 PM
To: Greg Bonifield; Graham, Mary
Cc: 'Horwitz, Richard L.'; dmoore@Potteranderson.com1; Ray Nimrod; Aaron Kaufman; Pals, Mark A.; Hales, Bryan S.; Santhanam, Hari; Desh, George
Subject: Proposed pleading

Greg and Mary,

You asked to review our proposed amended pleading before you would tell us whether you would oppose a motion to amend our answer and counterclaims to add inequitable conduct. Attached is our proposed pleading. Note that it contains information designated as Highly Confidential by Plaintiffs.

Regarding your question as to timing, you will see that this amended pleading is based on recent discovery that was not available to us before the deadline in the Scheduling Order for amended pleadings and was prepared as soon as practicable after we had an opportunity to collect, review and analyze the information upon which it is based.

Please let us know as soon as possible whether you will oppose our proposed amendment and your basis for any opposition.

Regards,
Amanda

****
IRS Circular 230 Disclosure:
To ensure compliance with requirements imposed by the U.S. Internal Revenue Service, we inform you that any tax advice contained in this communication (including any attachments) was not intended or written to be used, and cannot be used, by any taxpayer for the purpose of (1) avoiding tax-related penalties under the U.S. Internal Revenue Code or (2) promoting, marketing or recommending to another party any tax-related matters addressed herein.

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****

****
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e-mail to postmaster@kirkland.com, and destroy this communication and all copies thereof, including all attachments.
****