United States Court of Appeals for the Federal Circuit

02-1026, -1027

BOEHRINGER INGELHEIM VETMEDICA, INC.,

Plaintiff-Cross Appellant,

v.

SCHERING-PLOUGH CORPORATION
and SCHERING CORPORATION,

Defendants-Appellants.

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Appealed from: United States District Court for the District of New Jersey

Senior Judge Harold A. Ackerman

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DECIDED: February 21, 2003

Before MAYER, Chief Judge, CLEVENGER and RADER, Circuit Judges.

CLEVENGER, Circuit Judge.

Schering-Plough Corporation and Schering Corporation ("Schering") appeal the judgment of the United States District Court for the District of New Jersey, finding United States Patent No. 5,476,778 ("'778 patent") infringed and not invalid. Boehringer Ingelheim Vetmedica, Inc. ("Boehringer"), the assignee of the '778 patent, cross-appeals based on the district court's claim construction. We find that substantial evidence supports the verdicts on

invalidity and infringement, and affirm the judgment of the district court.

BACKGROUND

Porcine Reproductive Respiratory Syndrome (PRRS) (also known as "Mystery Swine Disease" or Swine Infertility and Respiratory Syndrome), swept through commercial pig herds in the 1980s. A previously unknown disease, PRRS had its most pronounced effect on young and newborn piglets. Up to thirty percent of the piglets in litters from infected sows were stillborn, and up to eighty percent of piglets in infected herds died before weaning. '778 patent, cols. 1-2. The financial consequences to the commercial pig industry were severe.

Researchers seeking a cause for PRRS could not identify any known pathogen behind the epidemic (hence the name "Mystery Swine Disease"). Scientists at Boehringer were the first to solve the mystery, discovering that a previously unknown virus was responsible for the disease. Starting with tissue samples from diseased animals, Boehringer's scientists added extracts from the tissue samples to mammalian cell lines grown in culture and looked for evidence of viral growth in the cell cultures.

As described in the '778 patent (cols. 2-3), Boehringer began with a homogenate of lung, brain, spleen, liver, and kidney tissues from an infected piglet. Samples of this combined homogenate were then added to a panel of 15 different cultured mammalian cell lines. While viruses themselves are too small to see without the aid of an electron microscope, a viral infection often gives rise to morphological changes in the host cell. An observable change in a host cell due to viral infection is known as a cytopathic effect, or CPE. These changes may include cell rounding, disorientation, swelling or shrinking, death, or detachment from the culture surface, and are visible with ordinary microscopes as perturbations of the cultured cell monolayer. Boehringer's scientists found evidence of a virus present in PRRS-infected animals when they observed a CPE in cultured MA-104 embryonic monkey kidney cells, one of the 15 cell lines inoculated with PRRS homogenate.

Continued propagation of a virus requires that the virus be passaged, which entails removing an aliquot of the culture and adding it to a fresh culture of cells. Boehringer scientists passaged the PRRS virus eight times on MA-104 cells, and deposited a sample of the virus from the eighth passage with the American Type Culture Collection (ATCC), which assigned it deposit number VR-2332. See Boehringer Ingelheim Animal Health, Inc. v. Schering-Plough

Corp., 984 F. Supp. 239, 248-49 (D.N.J. 1997).

The '778 patent claims this process for growing and isolating the PRRS virus: inoculating cultured monkey cells with the PRRS virus, and incubating the inoculated cells until a CPE is observed. Boehringer's suit against Schering for infringement of the '778 patent arises from Schering's production of its PrimePac vaccine against PRRS. Schering, like Boehringer, developed a vaccine against PRRS by attenuating the PRRS virus in cell culture. Attenuation is a process wherein a virus is repeatedly passaged on a cultured cell line, sometimes under altered culture conditions (such as lowered temperature). Variant viruses that are better adapted to grow on the cultured cell line will grow faster than the original virus; after many serial passages, such a variant will completely replace the original in the culture. Frequently, however, those variants adapted to grow in a particular environment (such as cultured monkey kidney cells) are ill-suited to grow or cause disease in the original environment (a live pig). If the attenuated virus will not productively infect pigs, but retains enough structural similarity to the original virus such that an immune response mounted against the attenuated virus will protect the pig against the original virus, then the attenuated virus may be used as a vaccine to protect against PRRS. Both Boehringer and Schering developed attenuated viruses effective as vaccines against PRRS.

Boehringer filed suit against Schering in the District Court for the District of New Jersey, alleging that Schering's vaccine virus, which is also grown on MA-104 monkey kidney cells, was prepared by a process that infringed the method claimed by the '778 patent. Upon Boehringer's motion for a preliminary injunction, the district court conducted a Markman hearing and construed the claim terms "isolating," "swine infertility and respiratory syndrome virus, ATCC-VR2332," and "incubating . . . until CPE is observed." Boehringer, 984 F. Supp. at 247-53. The court's construction of the "until CPE is observed" limitation precluded a finding of literal infringement, because Schering's vaccine production process measures the incubation period by time, rather than by level of CPE achieved. Boehringer Ingelheim Animal Health, Inc. v. Schering-Plough Corp., 6 F. Supp. 2d 324, 331 (D.N.J. 1998). However, this construction left open the possibility of infringement under the doctrine of equivalents. Id. at 331-32.

While the district court did not find that Schering's inequitable conduct defense posed an obstacle to Boehringer's request for a preliminary injunction, Boehringer, 984 F. Supp. at

261-62, the district court held that Boehringer had not met its burden of showing that Schering's obviousness challenge lacked substantial merit. Id. at 253-59. Nor had Boehringer established irreparable harm. Id. at 262-64. The district court therefore denied Boehringer's motion for a preliminary injunction.

Following the denial of various motions for summary judgment, Boehringer, 6 F. Supp. 2d at 332-37, the district court severed Schering's inequitable conduct defense from the infringement and obviousness issues, and in a ruling which Schering has not appealed, held that Boehringer had not engaged in inequitable conduct during prosecution of the '778 patent. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 106 F. Supp. 2d 667 (D.N.J. 2000). The issues of infringement (pared down to two questions of equivalence) and obviousness were submitted to a jury, which found for Boehringer on both issues. The district court denied Schering's motions for JMOL or a new trial, Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 166 F. Supp. 2d 19 (D.N.J. 2001), and entered judgment for Boehringer. The district court also issued an injunction prohibiting Schering not only from selling the accused vaccines, but also from "literally or equivalently infringing the '778 Patent" or "directly or indirectly using the method of Claim 2 of the '778 Patent."

Schering appeals the denial of its motion for JMOL, asserting that the district court incorrectly construed the claims and that the jury's verdict was not supported by substantial evidence. Boehringer cross-appeals, contending that the district court construed the "until CPE is observed" limitation too narrowly. We exercise jurisdiction over the appeals pursuant to 28 U.S.C. § 1295(a)(1).

I

We review the district court's claim construction de novo, as a matter of law. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1174 (Fed. Cir. 1998) (en banc). Claim 2 is the only claim at issue in this case, and depends from claim 1:

> 1. A method of growing and isolating swine infertility and respiratory syndrome virus, ATCC-VR2332, which comprises inoculating the virus on a full or partial sheet of simian cells in the presence of serum in a suitable grown medium and incubating the inoculated cell sheet at about 34° C. to 37° C. until CPE is observed.
>
> 2. The method as recited in claim 1 wherein the simian cell line is MA-104.

A. "Isolating"

The first dispute over claim construction concerns whether the term "isolating" recited in the claim's preamble imposes a limitation on the claim. While Schering, as we shall see, argues that the district court construed "isolating" too broadly, Boehringer asserts that the district court erred by treating "isolating" as a claim limitation at all. According to Boehringer, "isolating," as well as "growing," are mere recitations of purpose and as such do not impose any limitations on the method defined by the balance of the claim.

Boehringer is correct in that a preamble simply stating the intended use or purpose of the invention will usually not limit the scope of the claim, unless the preamble provides antecedents for ensuing claim terms and limits the claim accordingly. C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1350, 48 USPQ2d 1225, 1230-31 (Fed. Cir. 1998). Neither "growing" nor "isolating" is required to provide antecedent basis for subsequent claim language.

An intended use or purpose usually will not limit the scope of the claim because such statements usually do no more than define a context in which the invention operates. But as we explained in Griffin v. Bertina, 285 F.3d 1029, 62 USPQ2d 1431 (Fed. Cir. 2002), preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. Id. at 1033, 62 USPQ2d at 1434. This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the raison d'être of the claimed method itself. Divorced from the process of growing and isolating virus, the claimed method reduces to nothing more than a process for producing cytopathic effects in sheets of cultured MA-104 cells—a process whose absence of fathomable utility rather suggests the academic exercise. Gauging the effect of preamble language based on the claim as a whole, see Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620, 34 USPQ2d 1816, 1819-20 (Fed. Cir. 1995), it becomes apparent that claim 2 is in fact directed to a process for growing or isolating viruses. Accordingly, the district court properly recognized "isolating" as part of the definition of the claimed subject matter and thereby a limitation of the claim.

Having concluded that the district court correctly read "isolating" as imposing a limitation on the claim, we also conclude that the district court gave the term its proper construction. Essentially adopting Boehringer's interpretation, the district court held that the virus is "isolated" not only when the virus is cultured from tissues of an infected animal (the initial

recovery of the virus), but also during subsequent serial passages of the virus, when the virus is cultured from an aliquot of an infected cell culture. Boehringer, 984 F. Supp. at 248. In other words, PRRS virus is "isolated" according to claim 2 each time the virus is propagated into a fresh tissue culture bottle, not just when the virus is initially isolated from an infected pig.

Schering, however, contends that "isolating" can refer only to the initial growth of virus from an infected tissue sample or other natural source, and not to subsequent passages in culture. Under such a construction, Schering would escape infringement because Schering "isolated" the virus from infected pigs in 1991, before the '778 patent issued. Moreover, while Schering grows its attenuated vaccine virus on MA-104 cells, Schering initially isolated the PRRS virus on cultured porcine lung cells, rather than the simian cells required by the '778 claims.

The first step in claim construction is to determine the ordinary and customary meaning, if any, that would be attributed to the term by those skilled in the art. Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342, 60 USPQ2d 1851, 1854 (Fed. Cir. 2001). Dictionary definitions frequently are useful in this process, Tex. Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1202-03, 64 USPQ2d 1812, 1818-19 (Fed. Cir. 2002), and in support of its construction the district court cited a "common definition" of "isolate" found in the Random House College Dictionary: "to set or place apart, detach or separate." Boehringer, 984 F. Supp at 248. From this definition, the district court concluded that the PRRS virus was "isolated" in each serial passage, when the virus was separated from the infected cells.

According to Schering, however, the district court's reliance on this definition was erroneous. Because a term's ordinary meaning is that which it assumes in the field of the invention, Toro Co. v. White Consol. Indus., Inc., 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999), Schering contends that the district court should have looked instead to narrower definitions found in dictionaries of microbiology and molecular biology—some of which define "isolation" as the process of obtaining a pure culture from a naturally occurring population. Under such a definition, serial passaging of a virus during cell culture would not constitute "isolating."

Boehringer points out that Schering's technical definitions were not introduced into the record at trial, nor, apparently, were they in any way presented to the district court. Like trial

judges, we are free to consult dictionaries regardless of whether they have been offered by a party in evidence or not. Tex. Digital, 308 F.3d at 1203, 64 USPQ2d at 1819. Nonetheless, parties are obliged to make their claim construction arguments in the first instance to the district court, and we will rarely give weight to arguments that rely on sources brought forth for the first time on appeal. But Schering's technical dictionary definitions would carry little weight even if they had been first presented to the district court. Schering leads off its argument with the following technical definition of "isolation":

(microbiol.) Any procedure in which a given species of organism, present in a particular sample or environment, is obtained in pure culture.

Dictionary of Microbiology and Molecular Biology 468 (2d ed. 1987) (emphases added). Plainly, this definition does not require that the organism originate in a sample containing a natural or mixed population, and therefore easily encompasses propagation of a virus during serial passage, in which the virus is obtained from a culture comprising viruses, uninfected cells, infected cells, and dead cells. And while some of Schering's technical definitions do refer to obtaining organisms from natural populations, the remainder establish that the customary meaning of "isolating" in the field of the invention is broader than Schering maintains. The district court therefore properly determined that the ordinary meaning of "isolating" encompasses more than the initial isolation of a virus from an infected tissue sample.

While there is a strong presumption that the ordinary and accustomed meaning of a claim term governs its construction, this presumption may be overcome by evidence from the specification or prosecution history showing that the patentee employed the term in a manner inconsistent with its ordinary meaning. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325-26, 63 USPQ2d 1374, 1380-81 (Fed. Cir. 2002). Schering contends that both the patent's specification and prosecution history show reliance on a narrower meaning of "isolating," but its arguments are not persuasive. Under the heading "ISOLATION," the specification discloses both the culturing of tissue homogenate from infected animals, and several subsequent passages of the virus in culture. '778 patent, col. 2, l. 42 – col. 3, l. 54. Thus, to the extent that the specification uses a form of the verb "isolate," the specification supports the broader meaning of "isolating" advanced by Boehringer rather than the narrower construction advocated by Schering. Schering also points to the fact that the specification uses the word "recovered" as a synonym for "isolated," and uses the term "recover" only when referring to culture of the virus from tissue samples. But this observation strengthens Boehringer's position, not Schering's: the use of a different word to describe the isolation of PRRS virus from infected tissue samples—"recover"—suggests that "isolate" does not refer solely to this process.

Schering's prosecution history argument is similarly unavailing. During prosecution, Boehringer submitted several publications to the Patent and Trademark Office to establish that ATCC-VR2332 was the virus that caused PRRS. Because these references use the words "isolate" and "isolation" to refer to the recovery of the virus from tissues of infected animals, Schering contends that the term "isolating" in the claims should be so limited. But while references submitted during prosecution may shed light on the ordinary and accustomed meaning of a claim term, a patentee does not renounce the ordinary meaning of a term merely by submitting a reference that employs a different meaning. Absent a reliance on the narrower meaning by the patentee during prosecution, the references' use of "isolating" in a narrower sense does not preclude the claim term from also encompassing steps subsequent to the initial isolation. The district court construed this term correctly.

B. "ATCC-VR2332"

The next claim term in dispute is "swine infertility and respiratory syndrome virus, ATCC-VR2332," which describes the virus employed in the method of claim 2. The term "ATCC-VR2332" derives simply from the deposit of the virus with the American Type Culture Collection (ATCC), which assigned the accession number 2332 to the virus upon receiving Boehringer's deposit. '778 patent, col. 2, ll. 37-40. The district court construed this term to mean the "specific strain of PRRS" deposited with the ATCC. Boehringer, 984 F. Supp. at 249. Schering argues that the term should be limited to disease-causing viruses only, which would exclude Schering's attenuated strain. Boehringer, in contrast, argues that the term should be expanded to cover "any PRRS virus," disease-causing or not, although Boehringer does not explain exactly what "any PRRS virus" would mean. We conclude that the district court again correctly chose the middle ground between the parties' contentions.

Schering's argument simply seeks to add another limitation ("disease-causing") to the claim, and such arguments rarely succeed. The district court's claim construction already specifies a disease-causing virus, since the viral strain deposited with the ATCC will indeed cause PRRS. Presumably, Schering seeks to add an explicit "disease-causing" limitation so that it may argue that a finding of equivalence would vitiate this limitation entirely. We are not persuaded. The specification, as Schering points out, does state that ATCC-VR2332 will cause disease when administered to pigs. See '778 patent, col. 4, ll. 19-21. However, the specification also refers to "modified or attenuated live ATCC-VR2332," id. at col. 5, l. 25, indicating that the term "ATCC-VR2332" does not by itself demand pathogenicity. At bottom, Schering's argument is based on a simple fallacy: given the premise that all PRRS is caused by "ATCC-VR332," all "ATCC-VR2332" must therefore cause PRRS. Because such an argument is logically unsound, the district court correctly rejected Schering's attempt to add an additional limitation to the claim.

Boehringer, on the other hand, urges that the district court erred by construing "ATCC-VR2332" too narrowly.[1] The district court construed the term to mean the particular strain of PRRS virus that Boehringer deposited with the ATCC, Boehringer, 984 F. Supp. at 252, although the district court did not explain exactly what properties must be shown to establish that an accused virus meets this definition. Boehringer argues that this construction was erroneous, and that the term "ATCC-VR2332" should be understood as a "prototype" or "generic" term for all PRRS viruses, rather than as a reference to the deposited strain.

We find Boehringer's arguments no more persuasive than Schering's on this point. Boehringer chose to claim its virus using the term "ATCC-VR2332," a term on its face referring to a particular ATCC deposit. Boehringer did not use the broader term "PRRS virus," nor did Boehringer attempt to claim the virus in terms of the more general functional and structural properties disclosed by the specification. Boehringer did not choose to define the term "ATCC-VR2332" in the specification, nor did Boehringer state that ATCC-VR2332 was a "generic" or "prototype" virus, nor did Boehringer assert that viruses related to but not identical to the isolated strain were within the scope of the invention. These choices must be held against it. We therefore conclude that the district court properly construed "ATCC-VR2332" to refer to the strain of virus deposited with the ATCC.

C. "Incubating . . . until CPE is observed"

Claims 1 and 2 require, after a sheet of simian cells has been inoculated with a viral sample, that the cell sheet be incubated at a defined temperature range "until CPE is observed," that is, until viral growth manifests itself in an observable perturbation of the cultured cells. The dispute over construction of this limitation is whether it defines only the minimum period for which the cells must be incubated, or whether it also establishes an ending point beyond which incubation is not permitted. Before the district court, Boehringer argued that this term requires that "the incubation period continue long enough for CPE to be observed, but that the process need not be stopped immediately after the first observation." Boehringer, 984 F. Supp. at 252. That is, under Boehringer's interpretation, all the claim requires is that incubation continue at least up to the point where some degree of CPE is observed. Schering, however, argued that "until CPE is observed" means that the incubation is stopped immediately upon first observation of CPE, and any incubation that continues longer does not infringe. Schering would presumably escape infringement under such a construction, even under the doctrine of equivalents, because Schering's timed incubation continues well past the point at which CPE first becomes observable.

The district court agreed with Schering that "until CPE is observed" requires the incubation period to stop upon observation of CPE. Drawing an analogy to a recipe for cooking a turkey, the court reasoned that an instruction such as "cook the turkey until the skin is browned" necessarily implies that the cook should stop once the skin is browned; else the turkey would be singed and blackened rather than browned. Id. Likewise, the court concluded that an instruction to incubate the cell sheet "until CPE is observed" requires that incubation be

stopped once CPE is observed.

The district court recognized, however, that in the embodiments disclosed in the specification, incubation does not halt immediately upon the first observation of CPE, but rather continues until "good" or "50-60%" CPE is observed. See, e.g., '778 patent col. 3, ll. 46-48; col. 6, ll. 28-30. To avoid a claim interpretation inconsistent with these embodiments, the district court interpolated the word "significant" into the claim: incubation must proceed until "there is a significant degree of CPE." Boehringer, 984 F. Supp. at 253 (emphasis added). While this claim construction precluded Boehringer from establishing literal infringement, because Schering incubates its cells for a defined period of time rather than until a particular level of CPE is observed, it left open the possibility that Schering's timing mechanism could meet this limitation by the doctrine of equivalents. Boehringer, 6 F. Supp. 2d at 331-32.

We think the untenability of the district court's claim construction is exposed by the court's need to interpolate "significant" into the claim to save its construction. While incubation must be stopped at some point to recover the virus for subsequent passages, and undoubtedly the yield of viral recovery may be optimized by stopping the incubation at a particular point, the claim does not include any language or limitation relating to degree of viral recovery (if any). The claim retains its utility even if incubation is continued past the point of "significant" CPE or good viral recovery. Rather than insert an additional limitation into the claim, the better course is to rely on a construction of "until . . . CPE is observed" that does not require such an interpolation. We hold that this limitation merely defines the minimum period for incubation of the inoculated cell sheet.

Boehringer argues correctly that because the claim language is open, employing the preamble term "comprising," the claimed method is open to additional steps. Thus, while the claim requires a minimal incubation time proceeding until the observation of CPE, additional periods of incubation after that point are not excluded. To use the district court's meleagrine analogy, one may add an additional step to the recipe: "continuing to cook the turkey until the skin is burned to a crisp." Such an additional step is permissible from the structure of the open claim language, and the district court's rejection of such a step was based on the premise that the claim's object is defeated if cooking proceeds too long. Because the utility of claim 1 is not premised on a particular stopping point, there is no barrier to additional incubation periods.

This error, the only one we find in the district court's thorough and skillful management of this case, was nonetheless harmless. As we explain below, substantial evidence supports the jury's finding that Schering's process satisfies this claim limitation under the doctrine of equivalents, even under an overly narrow claim construction. The question of whether Schering's process would literally infringe under the correct claim construction need not be resolved.

II

A finding of literal infringement having been precluded by the district court's construction of the claim limitations "until . . . CPE is observed" and "ATCC-VR2332," see Boehringer, 6 F. Supp. 2d at 331, the question of infringement under the doctrine of equivalents was presented to the jury. The jury was asked to render verdicts on the following two questions:

> Did Boehringer prove by a preponderance of the evidence that the swine infertility and respiratory syndrome virus, ATCC-VR2525, as used in Schering's process for the production of its PrimePac® vaccines is equivalent to the "swine infertility and respiratory syndrome virus, ATCC-VR2332" as used in Claim 2 of the '778 Patent?
>
> Did Boehringer prove by a preponderance of the evidence that the incubation period of 72 hours +/- 6 hours as used in Schering's process for the production of its PrimePac® vaccines is equivalent to the timing device of "until CPE is observed" as used in Claim 2 of the '778 Patent?

The jury answered "yes" to both questions, and the district court denied Schering's renewed motion for judgment as a matter of law to overturn these verdicts. Boehringer, 166 F. Supp. 2d at 31-36. Schering, proposing that no reasonable jury could have answered both questions in the affirmative, asks us to reverse the district court's denial.

We review a district court's denial of a motion for JMOL de novo by reapplying the JMOL standard. Cybor, 138 F.3d at 1454, 46 USPQ2d at 1172. We will reverse the district court's denial only if the jury's factual findings are not supported by substantial evidence, or if the legal conclusions implied in the jury's verdict cannot be supported by that evidence. Id. Moreover, in scrutinizing the evidence for support for the jury's findings, we must draw all reasonable inferences in favor of the nonmoving party (here Boehringer), and while our review is of the record as a whole, we must disregard all evidence favorable to the moving party that the jury was not required to believe. Reeves v. Sanderson Plumbing Prods., Inc., 530 U.S. 133, 150-51 (2000).

A. The "ATCC-VR-2332" limitation

Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are "insubstantial" to one of ordinary skill in the art. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997); Eagle Comtronics v. Arrow Communication Labs., Inc., 305 F.3d 1303, 1315, 64 USPQ2d 1481, 1488 (Fed. Cir. 2002). While no particular linguistic framework controls the inquiry, Warner-Jenkinson, 520 U.S. at 39-40, the insubstantial differences inquiry may be guided by determining whether the element in the accused device "performs substantially the same function in substantially the same way to obtain the same result" as the claim limitation. Graver Tank & Mfg. Co. v. Linde Air Prods Co., 339 U.S. 605, 608 (1950); Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 813, 62 USPQ2d 1781, 1785 (Fed. Cir. 2002). Schering argues on appeal that regardless of which framework is employed, no reasonable jury could find that Schering's VR2525 virus is equivalent to the ATCC-VR2332 viral strain recited by the claim in suit.

Under the "function-way-result" analysis, Schering focuses on the fact that ATCC-VR2332 is a pathogenic virus, causing PRRS, while VR2525 is not. Schering argues that this distinction precludes a finding of equivalence, because Schering's virus generates a protective immune response when administered to pigs, while a pig inoculated with ATCC-VR2332 develops PRRS. Thus, when administered to pigs, VR2525 resembles ATCC-VR2332 in neither function, way, nor result. Schering's argument, however, flies in the face of the basic principle that the relevant analysis is "of the role played by each element in the context of the specific patent claim," WarnerJenkinson, 520 U.S. at 40, not whether the accused element is capable of performing different roles than the claim element in other contexts. As we have refused Schering's suggestion to add a separate "disease-causing" limitation to the claim in suit, what happens when the virus is administered to a pig is irrelevant to the assessment of whether the two viral strains are equivalent in the in vitro culture method defined by claim 2. The jury was presented with expert testimony from which it could conclude that VR2525 plays the same role as VR2332 in performance of the claimed method. The fact that, in other contexts, VR2525 can perform other functions in different ways to yield a different result is not relevant.

Schering likewise relies on properties of VR2525 that are largely irrelevant to the claim in suit in an attempt to show that no reasonable jury could find that VR2525 lacks "substantial

differences" from the ATCC-VR2332 strain recited by the claim. Schering highlights the fact that ATCC-VR2332 makes pigs ill while VR2525 does not, the fact that VR2525 does not react with a particular monoclonal antibody reactive against ATCC-VR2332, and the fact that VR2525 grows poorly in pig lung macrophages while ATCC-VR2332 grows well. But these facts are simply not relevant to the equivalence inquiry because those properties of the virus are not pertinent to a method of growing and isolating the virus as defined by claim 2.

Schering's argument based on Hill-Rom Co. v. Kinetic Concepts, Inc., 209 F.3d 1337, 54 USPQ2d 1437 (Fed. Cir. 2000), is inapposite. In Hill-Rom, the patentee tried to argue that an element in an accused hospital bed still met the claim limitation "cushion," even though the accused element did not provide support or comfort to the patient. Although the claim did not recite such functions for the cushion, we affirmed the district court's finding of no equivalence because the term "cushion" (as construed by the court) "carries with it certain functional features as a matter of the definition of the term." Id. at 1343, 54 USPQ2d at 1442. While the cushion in a hospital bed must provide support and comfort to the patient, the properties possessed by ATCC-VR2332 but lacking in VR2525—the ability to cause disease in pigs or grow in pig alveolar macrophages—are entirely optional for a method of growing and isolating a PRRS virus, unless the limitation "disease-causing" is imported into the claim.

Schering further argues that a finding of no substantial differences is precluded by the evidence that there are at least 73 nucleotide differences between VR2525 and ATCC-VR2332 in a particular region of their RNA genomes. Schering's expert (as well as Boehringer's) noted that even a single nucleotide substitution can have a substantial effect on viral function. Schering proposes that in the face of this evidence, no reasonable jury could have concluded that two viruses having at least 73 nucleotide divergences lack substantial differences.

However, the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence, and Schering made no showing that any of these substitutions actually affected any property of the virus relevant to the claim at hand. While it may be reasonable to assume that genetic similarity is a relevant comparison between the viruses for purposes of the claimed method, the jury was presented with expert testimony that the two viral genomes are highly similar overall and that any differences between the two

are insignificant. A reasonable jury could easily rely on this testimony to conclude that the genetic differences between VR2525 and ATCC-VR2332 are insubstantial in the context of the claimed method.

Schering's last attempts to stave off the jury's finding of equivalence rely on prosecution history estoppel. These attempts are unavailing. Schering first argues that because Boehringer's claims to vaccines and methods of immunization were rejected by the Patent Office, Schering's virus, useful as a vaccine, cannot be reached under the doctrine of equivalents. But a patentee is not estopped from establishing infringement under the doctrine of equivalents merely because an accused infringer improves upon the claimed invention. Schering's virus may have many useful properties that ATCC-VR2332 does not, properties that Boehringer was not entitled to claim. Schering's virus does not cease to infringe on account of those properties.

Schering further asserts that Boehringer's original claims encompassing "all zoopathogenic mutants" of ATCC-VR2332 were rejected during prosecution,[2] thus placing zoopathogenic (disease-causing) mutants beyond the patent's reach. But Schering has lost no opportunity to press upon us that its virus is not zoopathogenic, and we decline to speculate whether, as Schering contends, an alleged surrender of zoopathogenic mutants also includes, "a fortiori," a surrender of nonzoopathogenic mutants.

Even under a more searching review of the factual basis for the findings of equivalence, we would conclude that Boehringer's evidence suffices to carry the burden of establishing infringement by a preponderance of the evidence. The district court correctly concluded that the jury's verdicts on equivalence for this limitation of the claim were supported by substantial evidence, and we affirm the district court's denial of Schering's motion for JMOL.

B. The "incubating . . . until CPE is observed" limitation

Schering's challenge to the finding of equivalence to the "incubating . . . until CPE is observed" limitation is also based in part on its construction of the term "isolating." Schering, relying on Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc., 98 F.3d 1563, 40 USPQ2d 1481 (Fed. Cir. 1996), asserts that because the "purpose" of observing CPE is only to confirm that a virus is present in a sample from a natural source, Schering's accused process, lacking such a purpose, cannot infringe under the doctrine of equivalents.

Even under Schering's preferred claim construction (and assuming such a purpose is present in the claim), Schering's argument would seem to be belied by its own vaccine production instructions, which require that CPE be monitored for the purpose of confirming viral growth. Regardless, Schering's argument cannot stand in light of our affirmance of the district court's construction of "isolating."

With respect to the "until . . . CPE is observed" limitation, we have no doubt that substantial evidence supports the jury's finding of equivalence, even under the district court's overly narrow construction. Aside from the documentary evidence suggesting that Schering actually observes and records the degree of CPE during its production process, although perhaps not as a cue to terminate the incubation, the jury was presented with expert testimony that Schering's practice of incubating the viral culture for a defined period of time performs the same function, in the same way, with the same result, as incubating the viral culture until a defined degree of CPE is observed. Schering ignores this testimony entirely, except to note that Boehringer's expert did not personally witness one of Schering's production runs. This fact being irrelevant to the determination of equivalence in this case, the jury was well-entitled to rely on this testimony and render a verdict that Schering's process satisfied the "incubating . . . until CPE is observed" limitation under the doctrine of equivalents. The district court properly denied Schering's motion for JMOL on these grounds.

III

The question of obviousness was also submitted to the jury, which returned a verdict that Schering had not proven by clear and convincing evidence that the '778 patent was invalid under 35 U.S.C. § 103. Schering again challenges the district court's denial of its motion for JMOL. Obviousness is a question of law based on underlying factual determinations. Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 872, 228 USPQ 90, 97 (Fed. Cir. 1985). However, because obviousness, like any other ground of invalidity, must be established by clear and convincing evidence, id., Schering's burden on appeal is doubly high: it must show that no reasonable jury could have failed to conclude that Schering's case had been established by clear and convincing evidence.

We conclude that Schering has not met that heavy burden. The case for obviousness rests on a number of prior art references describing the use of MA-104 monkey kidney cells for growing and isolating other animal viruses (including at least one porcine virus), and two references (Dea and Van Alstine) describing attempts to recover the Mystery Swine Disease agent by inoculating cell lines, including monkey kidney cell lines, with tissue homogenates from infected herds.

A showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success, see Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000), and the jury was entitled to conclude that such a showing had not been made. In particular, Schering cannot escape the fact that both Dea and Van Alstine do more than suggest that PRRS viruses could be isolated with monkey kidney cells: they report failure of such attempts. Dea reported the isolation of a different virus, encephalomyocarditis virus (EMCV), by using adult monkey kidney (Vero) cells, and suggested that EMCV might be the agent responsible for PRRS outbreaks in Quebec. Even more tellingly, Van Alstine cultured homogenates from infected herds on eight different cell lines, including the MA-104 embryonic monkey kidney cells recited by claim 2. But Van Alstine reported only the isolation of parvovirus and swine influenza virus (SIV), and put forth SIV "as one of the prime suspects for at least one of the causes of Mystery Pig Disease." Neither Dea nor Van Alstine succeeded in isolating a PRRS virus with monkey kidney cells.

While absolute certainty is not necessary to establish a reasonable expectation of success, In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), there can be little better evidence negating an expectation of success than actual reports of failure. See, e.g., In re Rinehart, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976). A reasonable jury could conclude from these reports that one of ordinary skill in the art would not have had a reasonable expectation of success in attempting to isolate the PRRS virus on MA-104 cells at the time the invention was made. Consequently, the district court did not err by denying Schering's motion for JMOL on the issue of obviousness.

CONCLUSION

We conclude that the district court correctly construed the '778 claims, with the exception of the "until CPE is observed" limitation, such error being harmless for purposes of the jury verdicts. The jury's verdict for Boehringer on infringement under the doctrine of equivalents, and its verdict against Schering on its obviousness challenge, were well-supported by substantial evidence. Schering was not entitled to judgment as a matter of law contrary to the jury's verdicts, and we therefore affirm the judgment of the district court.

AFFIRMED

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[1] Boehringer based its cross-appeal on the district court's claim construction ruling and associated summary judgment order—an order which did not address the "ATCC-VR2332" limitation. Upon Schering's motion to dismiss the cross-appeal, Boehringer articulated a new rationale for its cross-appeal, arguing that the scope of the district court's injunction (and thus of Boehringer's rights) was limited by its erroneously narrow claim construction. While Boehringer's case for cross-appealability appears marginal, we decline to address the propriety of the cross-appeal. Boehringer was, of course, free to advance its rejected claim construction arguments as alternative grounds for affirmance. United States v. Am. Ry. Exp. Co., 265 U.S. 425, 435 (1924). "Cross-appeals for the sole purpose of making an argument in support of the judgment are worse than unnecessary. They disrupt the briefing schedule, increasing from three to four the number of briefs, and they make the case less readily understandable to the judges. The arguments will be distributed over more papers, which also tend to be longer. Unless a party requests the alteration of the judgment in its favor, it should not file a notice of appeal." Jordan v. Duff & Phelps, Inc., 815 F.2d 429, 439 (7th Cir. 1987). These comments are doubly appropriate when parties overlay their dispute with a further quarrel regarding the propriety of a cross-appeal.

[2] Boehringer disputes the version of the prosecution history put forth in both of Schering's arguments. Because we do not find Schering's arguments persuasive even under its version of the prosecution history, we need not resolve this dispute.