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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DEREK O'HAGAN¹

Appeal 2014-003920
Application 12/092,146
Technology Center 1600

Before DONALD E. ADAMS, TAWEN CHANG, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an immunogenic composition comprising a split influenza virus antigen and a Th1 adjuvant, which have been rejected as anticipated or obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm in part, designate the affirmance-in-part a new ground of rejection, and further enter a new ground of rejection under 37 C.F.R. § 41.50(b).

¹ Appellant identifies the Real Party in Interest as Novartis Vaccines and Diagnostics, Inc. (Appeal Br. 2.)

STATEMENT OF THE CASE

Influenza vaccines can be based on inactivated “split” virus. (Spec. 1:7–9.) Such “split” vaccines are obtained by treating virions with detergents to produce subvirion preparations (i.e., preparations comprising incomplete viral particles). (*Id.* at 1:12–13.) The Specification states that an oculorespiratory syndrome (ORS) has been observed in patients who received certain split vaccines, where “[t]he ORS has been associated with incomplete splitting of virions during manufacture, giving compositions with a high proportion of microaggregates of unsplit virions.” (*Id.* at 1:16–19.) The Specification also states that, while “[t]here is no causal explanation of the link between split vaccines and ORS, . . . it has been proposed that the vaccine may upset the natural Th1/Th2 balance, with the particulate unsplit virions causing a bias towards a Th2 phenotype.”² (*Id.* at 1:22–25.) According to the Specification, “an object of the invention [is] to minimize the risk that a split influenza vaccine might elicit ORS.” (*Id.* at 1:20.) Further according to the Specification, this object may be accomplished by an immunogenic composition comprising “a split influenza virus antigen and an adjuvant, wherein (a) the antigen is prepared from a virus grown in cell culture, and (b) the adjuvant does not consist solely of aluminum salts.” (*Id.* at 2:15–17.)

Claims 1–9, 11–29, and 32 are on appeal. Claims 1 and 29 are the only independent claims and are reproduced below:

Claim 1: An immunogenic composition comprising a split influenza virus antigen and a Th1 adjuvant, wherein the antigen is prepared from a virus grown in cell culture and does not include any egg proteins and the Th1 adjuvant is in the form of

² Th1 and Th2 refer to, respectively, Type 1 and Type 2 T helper cells.

(i) an oil-in-water emulsion which includes squalene, a tocopherol, and polysorbate 80, or (ii) a submicron oil-in-water emulsion of squalene, polysorbate 80, sorbitan trioleate, and an immunostimulatory oligonucleotide.

Claim 29: An immunogenic composition comprising a split influenza virus antigen and an oil-in-water emulsion, wherein (a) the antigen is prepared from a virus grown in an MDCK cell culture, and (b) the oil-in-water emulsion includes a tocopherol.

(Appeal Br. 21 and 23 (Claims App'x).)

The Examiner rejects claims 1, 8–11, 16–18, 22, 23, 29, and 32 under 35 U.S.C. § 102(b) as anticipated by Friede.^{3,4} (Ans. 2.)

The Examiner rejects claims 5–7, 11–15, 17–28, and 32 under 35 U.S.C. § 103(a) as unpatentable over Friede, Hoffman,⁵ Van Scharrenburg,⁶ and Smith,⁷ as evidenced by Tween 80 Product Information Sheet.⁸

(Ans. 3.)

I.

Issue

The Examiner has rejected claims 1, 8–11, 16–18, 22, 23, 29, and 32 under 35 U.S.C. § 102(b) as anticipated by Friede. The Examiner finds that

³ Friede et al., US 6,544,518 B1, issued Apr. 8, 2003 (“Friede”).

⁴ Although both the Examiner and Appellant includes claim 30 in the discussion of the anticipation rejection over Friede (Ans. 2; Appeal Br. 3), claim 30 has been cancelled (Appeal Br. 24 (Claims App'x); June 16, 2011 Amendment 6). Accordingly, we do not consider claim 30 in this appeal.

⁵ Hoffman, US 6,951,754 B2, issued Oct. 4, 2005 (“Hoffman”).

⁶ Van Scharrenburg et al., US 5,948,410, issued Sept. 7, 1999 (“Van Scharrenburg”).

⁷ Smith et al., US 6,245,532 B1, issued June 12, 2001 (“Smith”).

⁸ Sigma-Aldrich, Product Information Sheet for Tween® 80 Sigma Ultra, CAS Number 9005-65-6, Product Number P 8074 (“Tween 80 Product Information Sheet”).

“Friede discloses an immunogenic composition comprising split influenza virus antigen prepared from a virus grown in MDCK cells and comprising a[] Th1 adjuvant and an oil-in-water emulsion including a tocopherol and particularly a DL-[alpha]-tocopherol, polysorbate 80 and squalene.” (Ans. 2.) Appellant contends that Friede does not anticipate because “extensive picking and choosing from the disclosures in the reference would be required.” (Appeal Br. 3–6.)

The issue with respect to this rejection is whether Friede discloses all elements of claims 1 and 29 arranged as in the claims.

Findings of Fact

1. Friede’s invention relates to adjuvant compositions . . . suitable to be used in vaccines. In particular, the adjuvant compositions . . . comprises a saponin and an immunostimulatory oligonucleotide Also provided by the present invention are vaccines comprising the adjuvants of the present invention and an antigen.

(Friede Abstract; *see also id.* at 1:6–18.)

2. Friede discloses that “immunostimulatory oligonucleotides (CpG) and saponin combinations are extremely potent adjuvants.” (Friede 2:54–56.)⁹

3. Friede discloses a preferred form of its invention in which “the saponin and oligonucleotides in the adjuvant and vaccine compositions act

⁹ CpG is “an abbreviation for cytosine-guanosine dinucleotide motifs present in DNA.” (Friede 1:23–24.) Saponins are “steroid or triterpene glycosides widely distributed in the plant and marine animal kingdoms.” (*Id.* at 1:62–63.) Friede discloses that useful saponins include those derived from the tree bark of *Quillaja Saponaria Molina*, referred to as Quil A, and fractions thereof such as QS21. (*Id.* at 3:41–48.)

synergistically in the induction of antigen specific antibody and are potent in the induction of immune responses conventionally associated with the Th1-type immune system.” (*Id.* at 2:59–65.)

4. Friede discloses that “the CpG/saponin combinations . . . may be further combined with other adjuvants including lipopolysaccharide [(LPS)] or a derivative thereof.” (*Id.* at 6:28–31.)

5. Friede discloses that, “[p]referably, the adjuvants of the present invention may further comprise a carrier.” (*Id.* at 2:58–59; *see also id.* at 4:1–6.)

6. Friede discloses that the carrier may be in the form of an oil in water emulsion. (*Id.* at 4:7–14, 4:19–24, 8:21–22.) Friede further discloses that

[m]ost preferably, the adjuvant combination comprises [certain enumerated CpG sequences] mixed with [saponin] QS21, and a particulate carrier selected from the group comprising an oil-in-water emulsion or DQ. Accordingly, particularly preferred vaccines, for example, comprise such adjuvant combinations and an antigen.

(*Id.* at 4:39–50; *see also* 5:14–19.)¹⁰

7. Friede discloses that

[s]qualene . . . is an unsaturated oil . . . and is a particularly preferred oil for use in this invention. Particularly preferred oil emulsions are oil in water emulsions, and in particular squalene in water emulsions.

In addition, the most preferred oil emulsion adjuvants of the present invention comprise an antioxidant, which is preferably the oil α -tocopherol.”

(*Id.* at 8:54–67.)

¹⁰ “QS21 (5 μ g) mixed with liposomes in a weight ratio of QS21/cholesterol of 1/5” is referred to as DQ. (*Id.* at 24:10–12.)

8. Friede discloses a prior art “adjuvant emulsion system based on squalene, α -tocopherol and polyoxyethylene sorbitan monooleate (TWEEN80), formulated with the immunostimulant QS21, [a saponin,] optionally with [LPS-derivative] 3D-MPL.” (*Id.* at 8:1–5, 2:18–21, 6:38–7:1; *see also* 9:1–4.)

9. Friede discloses that [t]he size of the oil droplets found within the stable oil in water emulsion are preferably less than 1 micron, may be in the range of substantially 30-600 nm, preferably substantially around 30-500 nm in diameter, and most preferably substantially 150-500 nm in diameter, and in particular about 150 nm in diameter as measured by photon correlation spectroscopy. (*Id.* at 9:9–15.)

10. Friede discloses that [t]he amounts of the components present in the oil emulsions of the present invention are conventionally in the range of from 2 to 10% oil, such as squalene; and when present, from 2 to 10% alpha tocopherol; and from 0.3 to 3% surfactant, such as polyoxyethylene sorbitan monooleate. Preferably the ratio of oil: alpha tocopherol is equal or less than 1 as this provides a more stable emulsion. Span 85 may also be present at a level of about 1%. (*Id.* at 9:19–26.)

11. Polyoxyethylene sorbitan monooleate is also referred to as Tween 80. (*Id.* at 8:3; Spec. 17:16.) Appellant has not disputed that Tween 80 is the same compound as polysorbate 80. (Ans. 9; *see also* Spec. 17:5–7.)

12. Span 85 is also referred to as sorbitan trioleate. (Spec. 17:14.)

13. Friede discloses that [p]referably the vaccine formulations of the present invention contain an antigen or antigenic composition capable of eliciting an immune response against a human pathogen, which antigen or antigenic

composition is derived from [e.g.,] Influenza virus (whole live or inactivated virus, split influenza virus, grown in eggs or MDCK cells, or whole flu virosomes . . . or purified or recombinant proteins thereof, . . . or combinations thereof).

(Friede 9:46–10:3.)

Analysis

In response to Appellant’s argument that extensive picking and choosing from among Friede’s disclosures would be needed to arrive at the claimed inventions, the Examiner counters that Friede discloses a vaccine composition comprising all three components of the claimed Th1 adjuvant—squalene, tocopherol, and polysorbate 80. (Ans. 9.) The Examiner further argues that Friede discloses that the “vaccine formulations of his invention *preferably* contain antigens eliciting an immune response against a human pathogen such as split influenza virus antigen grown in MDCK cells.” (*Id.* at 9–10.) The Examiner thus contends that “one of skill in the art would at once envisage the claimed composition because the presently claimed components are preferred elements of the prior art composition.” (*Id.* at 10.)

We find Appellant to have the better argument. Friede teaches, at separate locations of the reference, each of the elements of claims 1 and 29, including an immunogenic composition comprising a split influenza virus antigen (FF13), an influenza virus grown in MDCK cells (*id.*), and a Th1 adjuvant (FF3) comprising an oil-in-water emulsion that includes squalene, a tocopherol, and polysorbate 80 (FF5–FF11). However, Friede does not teach a single embodiment with each of the claimed elements despite noting a preference for squalene in an oil emulsion adjuvant and a preference for including α -tocopherol as an antioxidant in an oil emulsion. Instead, arriving at the invention from Friede’s disclosures requires selection of the

elements from a variety of disclosed immunogens and various adjuvant compositions. (*See, e.g.*, Friede 9:46–10:65 (possible antigens include a reference to influenza virus), 9:65–10:3 (possible flu virus including “whole live or inactivated virus, split influenza virus, grown in eggs or MDCK cells, or whole flu virosomes . . . or purified or recombinant proteins thereof . . . or combinations thereof”), 2:53–65 (noting the adjuvants of the invention include CpG and saponin combinations along with a carrier without specifying a requisite carrier), 7:65–9:28 (providing a variety of emulsion systems and carriers that may be combined with the saponin and CpG components of the adjuvant including liposomes and water in oil emulsions besides oil based emulsions).) With respect to the Examiner’s argument that a skilled artisan would “at once envisage the claimed composition because the presently claimed components are preferred elements of the prior art composition” (Ans. 10), we note in particular that, while Friede teaches that its vaccine formulations preferably contain an antigen capable of eliciting an immune response against particular human pathogens, including antigens derived from the influenza virus, Friede neither singles out such antigens from others listed nor expressed a preference for a particular form of antigen (e.g., split virus grown in MDCK cells). (FF13.)

An anticipatory reference under 35 U.S.C. § 102

must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.

Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter

which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection.

In re Arkley, 455 F.2d 586, 587-588 (CCPA 1972).

Here, as in *Arkley*, the rejection would require picking and choosing from parts of Friede's disclosure in order to arrive at the claimed invention. Such picking and choosing is not consistent with anticipation.

Accordingly, we reverse the Examiner's rejection of claims 1 and 29 under 35 U.S.C. § 102(b) as anticipated by Friede. The rejection of claims 8–11, 16–18, 22, 23, and 32, which depend directly or indirectly from claim 1, are likewise reversed.

II.

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new grounds of rejection: Claim 1 and 29 are rejected under 35 U.S.C. § 103(a) as obvious over Friede.

Analysis

As discussed above, Friede teaches each of the elements of claims 1 and 29, albeit at separate locations in the reference. In particular, Friede teaches vaccines comprising an antigen and an adjuvant composition comprising a saponin and an immunostimulatory oligonucleotide. (FF1.) Friede teaches that the antigen may be a split influenza virus grown in MDCK cells. (FF13.) Friede teaches a preferred form of its invention where “the saponin and oligonucleotides in the adjuvant and vaccine compositions . . . are potent in the induction of immune responses conventionally associated with the Th1-type immune system.” (FF3.)

Friede also teaches that the saponin/oligonucleotide combination of its invention may be combined with other adjuvants and preferably further comprise a carrier, which may be in the form of an oil in water emulsion. (FF4–FF6.) Friede discloses that “[t]he size of the oil droplets found within the . . . oil in water emulsion are preferably less than 1 micron.” (FF9.) Friede teaches that “[p]articularly preferred oil emulsions are . . . squalene in water emulsions” and states in addition that “the most preferred oil emulsion adjuvants of the present invention comprise an antioxidant, which is preferably the oil α -tocopherol.” (FF7.)

Finally, Friede discloses that “[t]he amounts of the components present in the oil emulsions of the present invention are conventionally . . . from 2 to 10% oil, such as squalene; and when present, from 2 to 10% alpha tocopherol; and from 0.3 to 3% surfactant, such as polyoxyethylene sorbitan monooleate[, i.e., Tween 80 or polysorbate 80]. . . . Span 85[, i.e., sorbitan trioleate,] may also be present at a level of about 1%.” (FF10–FF12.)

Appellant argues (in response to the Examiner’s obviousness rejection over Friede, Hoffman, Van Scharrenburg, and Smith) that there is no reason for a skilled artisan to combine the disclosures in Friede to arrive at the claimed invention:

The Examiner has not cited to any portion of any of Friede et al., Hoffman, Scharrenburg et al., and Smith et al. or from the general knowledge in the art that would give one of skill in the art a reason to: (i) pick an influenza antigen from the list of over 100 different organisms in addition to influenza viruses . . . ; (ii) select split virus antigen from at least six antigen forms including whole live virus, whole inactivated virus, split virus, whole flu virosomes or purified or recombinant virus antigens; (iii) select MDCK cell culture of the virus from culturing virus in egg or MDCK cells; (iv) elect to add an optional carrier, (v) pick an oil-in-water emulsion from the carriers,

which include micelles, ordered structures such as ISCOMS, liposomes, oil-in-water emulsions, metallic salts (which are actually preferred), and particulate carriers such as chitosan, and (vi) pick an oil-in-water emulsion that meets the limitations of one of the claimed alternative Th1 adjuvants from the various formulations of oil-in-water emulsions discussed by Friede et al.

(Appeal Br. 14.)

We are not convinced. As explained in *KSR*, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). In this case, we find that it would be obvious for a skilled artisan to combine Friede’s various disclosures, which particularly point out that a mixture of squalene, α -tocopherol, polysorbate 80 that can also include immunostimulants is a known adjuvant mixture that could be used with the antigenic materials disclosed and also indicates a preference for using squalene as the oil in an oil-in-water emulsion adjuvant and including α -tocopherol as an antioxidant in such composition (FF7, FF8), with a reasonable expectation of success in arriving at the claimed invention, because such combination is no more than “the predictable use of prior art elements according to their established functions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416–417 (2007).

Appellant also argues that there can be no motivation to combine because Friede provides no information regarding what adjuvants are Th1 adjuvants and provides no guidance on which antigens cause an excessive Th2 response. (Appeal Br. 15.) Thus, according to Appellant, “a person of skill considering Friede . . . would have no information regarding which of the many antigens . . . to combine with a Th1 adjuvant in order to achieve a balanced Th1/Th2 response.”

This argument is likewise unpersuasive. “In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. . . . [A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007). As discussed above, it would be obvious to a skilled artisan to combine the various disclosures in Friede to arrive at the claimed invention; thus, claims 1 and 29 are obvious regardless of whether Friede discloses the same problem allegedly solved by the claimed invention.

Finally, Appellant argues that the claimed subject matter exhibits unexpected results because the cited art does not teach or suggest the problem addressed by the claimed invention or the claimed solutions. (Appeal Br. 11–13.) In particular, Appellant argues that the claimed invention lowers the risk of ORS by stimulating a Th1 response and by using virus that does not contain any egg proteins, while the cited references neither disclose the risk of ORS nor suggest the claimed solutions. (*Id.* at 11–12.) Appellant further argues that, although an influenza antigen may provoke either a Th1 or Th2 response depending on whether the antigen was produced in eggs or in cell culture and whether it is a whole virus or a split antigen (*id.* at 13), the cited references do not teach which adjuvants are Th1 adjuvants or “which split influenza virus antigens can cause an excessive Th2 response” (*id.* at 12).

We do not find this argument persuasive. Appellant has not cited any evidence that the results achieved by the compositions of claims 1 and 29 are *unexpected*, much less unexpected as compared to the closest prior art

compositions of Friede. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”). Appellant’s “unexpected results” boil down to the argument that the cited art does not disclose the problem allegedly solved by the claimed invention. As already discussed, however, Appellant’s particular motivation and avowed purpose in arriving at the claimed invention do not control the obviousness inquiry. *KSR*, 550 U.S. at 419–20.

III.

Issue

The Examiner has rejected claims 5–7, 11–15, 17–28 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Friede, Hoffman, Van Scharrenburg, and Smith, as evidenced by the Tween 80 Product Information Sheet. As discussed above, the Examiner finds that “Friede discloses an immunogenic composition comprising split influenza virus antigen prepared from a virus grown in MDCK cells and comprising an Th1 adjuvant and an oil-in-water emulsion including a tocopherol and particularly a DL-[alpha]-tocopherol, polysorbate 80 and squalene.” (Ans. 2–3.) The Examiner finds that Friede does not teach

the composition containing less than 10 ng of DNA that is 100 nucleotides or longer [(claim 6);] between 0.1 and 20 µg of haemagglutinin antigen per viral strain [(claim 7);] serum free cell culture [(claim 15);] the composition substantially free from mercurial material [(claim 19);] the composition including between 1 and 20 mg/ml sodium chloride [(claim 20);] or having osmolality between 200 and 400 m[theta]sm/kg [(claim 21);] or containing less than 1 endotoxin unit per dose [(claim 25)]. Friede does not teach the composition comprising split influenza virus antigen prepared from an

influenza virus [having one or more] RNA segments from an A/PR/8/34 [] influenza virus [(claim 12)].

(*Id.* at 3.)

The Examiner finds, however, that

Hoffman teaches an immunogenic composition comprising split influenza virus antigen prepared from an influenza virus RNA segments from an A/PR/8/34 H1 influenza virus grown on MDCK and Vero cells and a Th1 adjuvant. Hoffman teaches that his composition is free of the host cell cellular DNA and it therefore contains less than 10 ng of cellular DNA. Hoffman teaches that the virus antigen is prepared from an influenza virus obtained by reverse genetics techniques. Hoffman teaches cell suspension culture. Hoffman teach[es] a monovalent vaccine against a pandemic influenza virus strain.

[Van] Scharrenburg teaches an immunogenic composition comprising split influenza virus antigen grown in MDCK cells comprising less than 10 ng of DNA 100 nucleotides or longer.

(*Id.* at 4 (citations omitted.) The Examiner further finds that “Smith teaches growing influenza virus in serum-free culture of MDCK cells, and wherein the composition is substantially free from mercurial material.” (*Id.* (citation omitted).)

The Examiner concludes that it would have been prima facie obvious to provide the composition disclosed in Friede further comprising the dependent claim limitations at issue in light of the disclosures in Hoffman, Van Scharrenburg, and Smith. (*Id.* at 4–5.) In particular, the Examiner finds that “the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results.” (*Id.* at 5–6.) The Examiner further finds that “[i]t would have been obvious to optimize the amounts and

concentrations of the adjuvant components and the size of the oil droplets” in the emulsion. (*Id.* at 5.)

Appellant contends that there is no reason to combine the prior art elements as claimed. (Appeal Br. 13–15; Reply Br. 9–10 and 12–14.) Appellant further contends that “the claimed invention produces a surprising result that rebuts any prima facie case of obviousness.” (Appeal Br. 11–13; Reply Br. 9 and 10–12.)

Appellant focuses attention on dependent claim 5. Accordingly, we limit our discussion to claim 5.¹¹ The issues with respect to this rejection are (1) whether the evidence of record supports the Examiner’s conclusion that claim 5 is prima facie obvious over Friede, Hoffman, Scharrenburg, and Smith, as evidenced by Tween 80 Product Information Sheet, and (2) if so, whether Appellant has provided evidence of unexpected results that, when weighed with the evidence for obviousness, renders claim 5 non-obvious.

Findings of Fact

14. Van Scharrenburg teaches that, for purposes of use in flu vaccines, “tissue culture derived production” of influenza virus has many advantages over influenza viruses “cultured on embryonated chicken eggs.” (Van Scharrenburg 1:30–59.)

15. Van Scharrenburg teaches that,
[n]evertheless, an important problem remains in relation to tissue culture of Influenza virus too, as genetic material from continuous cell lines may remain present in the vaccine.

¹¹ We address the obviousness rejection as it relates to claim 5 as argued on Appeal. In the event of further prosecution, the Examiner should also evaluate the merits of the remaining dependent claims not addressed herein.

Such problem poses a risk which, if not remedied, may lead regulatory authorities to decline requests for market allowance for such Influenza vaccines for safety reasons. E.g. the U.S. Food and Drug Administration demands that biotechnological products for human use do not contain more than 100 pg of host cell DNA per dose.

(Id. at 1:60–2:2.)

16. Van Scharrenburg teaches that its invention provides a method for the preparation of Influenza Virus surface antigen for vaccine purposes which is safe and does not contain nonacceptable amounts of deleterious genetic material, and meets the requirements set by the regulatory authorities. However, it was considered desirable and surprisingly also attainable to prepare influenza vaccines with a host cell DNA content considerably lower than 100 pg/dose.

Accordingly, the present invention is concerned with an Influenza surface antigen vaccine obtainable by production from Influenza Viruses propagated on animal cell culture and having a host cell DNA content equal to or less than 25 pg per dose.

(Id. at 2:3–15.)

17. Van Scharrenburg discloses [a] method for the preparation of surface antigen proteins useful for preparing such low DNA influenza vaccine from Influenza Viruses propagated on an animal cell culture comprising the subsequent steps of:

- a. treatment of whole virus containing fluid obtained from the cell culture with a DNA digesting enzyme, and
- b. adding a cationic detergent,

followed by isolation of the surface antigen proteins.

(Id. at 2:15–23.)

18. Van Scharrenburg discloses that the process according to its invention “yields a product which is extremely low in its content of animal cell-derived DNA. DNA concentrations as low as 25 pg/dose and in many

instances even as low as 10 pg/dose are easily attainable.” (*Id.* at 3:9–13; *see also id.* at 3:66–4:27, 4:41–50, claims 1 and 2.)

19. Hoffman teaches “a dual promoter system . . . for the efficient intracellular synthesis of viral RNA.” (Hoffman Abstract.) Hoffman teaches that “one application of the system is production of attenuated, reassortant influenza viruses for use as antigens in vaccines.” (*Id.*)

20. Hoffman teaches coculturing “human 293T cells . . . together with the standard cell line used for influenza A (MDCK-cells). Viruses produced in the 293T cells after transfection can then infect MDCK cells and replicate.” (*Id.* at 8:22–27.)

21. Hoffman teaches that “[v]accine safety is . . . a concern. Because the vaccines of the invention permit production in defined cell culture systems, they avoid non-specific pathogens, bacteria, and allergenic proteins that may be present in commercial vaccines prepared in embryonated eggs.” (*Id.* at 29:41–47.)

22. Hoffman teaches that

[t]he term “purified” . . . refers to material that has been isolated under conditions that reduce or eliminate the presence of unrelated materials, i.e., contaminants, including native materials from which the material is obtained. For example, a purified virion is preferably substantially free of host cell or culture components, including tissue culture or egg proteins, non-specific pathogens, and the like. As used herein, the term “substantially free” is used operationally, in the context of analytical testing of the material. Preferably, purified material substantially free of contaminants is at least 50% pure; more preferably, at least 90% pure, and more preferably still at least 99% pure. Purity can be evaluated by chromatography, gel electrophoresis, immunoassay, composition analysis, biological assay, and other methods known in the art.

Methods for purification are well-known in the art. . . . A purified material may contain less than about 50%, preferably less than about 75%, and most preferably less than about 90%, of the cellular components, media, proteins, or other nondesirable components or impurities (as context requires), with which it was originally associated. The term “substantially pure” indicates the highest degree of purity which can be achieved using conventional purification techniques known in the art.

(*Id.* at 22:49–23:8.)

23. Hoffman teaches using adjuvants, i.e., “a compound or mixture that enhances the immune response to an antigen,” with vaccines such as influenza vaccines. (*Id.* at 29:48–30:2.) Hoffman teaches that “[a]djuvants include, but are not limited to . . . saponin” and further teaches that “[a]n example of a preferred synthetic adjuvant is QS-21.” (*Id.* at 29:58–65.)

24. Hoffman teaches that “[v]accination effectiveness may be enhanced by co-administration of an immunostimulatory molecule . . . with the vaccine.” (*Id.* at 30:19–24.)

25. Smith relates to a method of preparing a recombinant influenza vaccine using DNA technology. (Smith Abstract.)

26. Smith teaches that “[t]he current manufacturing process for influenza vaccines . . . is limited by propagation of the virus [in] embryonated chicken eggs.” (*Id.* at 3:7–9; *see generally id.* at 3:9–44.) In particular, Smith teaches that

[a] method of producing an influenza vaccine that does not require propagation in eggs would result in a purer product that would be less likely to cause an adverse immune reaction. In addition, a purer vaccine preparation would not require virus inactivation or organic extraction of viral membrane components, thereby avoiding denaturation of antigenic epitopes and safety concerns due to residual chemicals in the vaccine.

In addition, an influenza vaccine produced in the absence of egg propagation would . . . result in a vaccine that is better matched with influenza epidemic strains, resulting in improved efficacy.

It is therefore an object of the present invention to provide a method of producing an influenza vaccine that does not require replication in eggs.

(*Id.* at 3:29–44.)

27. Smith teaches isolating influenza strains from individuals infected with the disease, propagating the strains in cells producing high viral titers, such as MDCK cells, and then purifying the viral particles. (*Id.* at 6:65–7:11 and 7:29–39.)

28. Smith teaches subsequently cloning influenza hemagglutinin genes into plasmid transfer vectors and transfecting the vectors into insect cells. (*Id.* at 7:40–8:21.) Smith further teaches expressing the recombinant hemagglutinin antigens in the insect cells and then extracting the antigens for use as a component of an influenza vaccine for human use. (*Id.* at 8:51–64 and 10:39–11:22.)

Analysis

Claim 5 depends from claim 1 and further requires that the claimed immunogenic composition contains less than 10ng of cellular DNA from the cell culture host. (Appeal Br. 21 (Claims App'x).) We agree with the Examiner that claim 5 is obvious over the combination of Friede, Hoffman, Van Scharrenburg, and Smith, as evidenced by the Tween 80 Product Information Sheet. As already discussed, Friede renders obvious the composition of claim 1. Each of Hoffman, Van Scharrenburg, and Smith also teaches the benefits of growing the influenza virus in cell culture rather than in embryonated egg for the purpose of vaccine development. (FF14,

FF21, FF26.) Van Scharrenburg further teaches a method for preparing influenza vaccines produced from influenza viruses “propagated on animal cell culture and having a host cell DNA content equal to or less than 25 pg per dose.” (FF16.)

As discussed above, we conclude that a skilled artisan would have considered it obvious to combine the prior art oil-in-water emulsion of squalene, α -tocopherol and polysorbate 80 disclosed in Friede with a split influenza virus antigen also disclosed in Friede to arrive at the invention of claim 1 as a predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 416–417. We further find that, in light of teachings in Van Scharrenburg, a skilled artisan would have reason to modify the composition suggested by Friede such that the composition contains less than 10ng of cellular DNA from the cells in which the influenza virus was cultured. In particular, Van Scharrenburg teaches that genetic material from cells in which the influenza virus is cultured poses a safety risk when present in the vaccine and also teaches that government regulators “demand[] that biotechnological products for human use do not contain more than 100 pg of host cell DNA per dose.” (FF15.) Likewise, a skilled artisan would have a reasonable expectation of success in achieving a claimed vaccine composition containing less than 10 ng of host cell DNA, as Van Scharrenburg teaches a process that results in vaccines having host cell DNA content equal to or less than 25 pg per dose. (FF16.)

Appellant contends that there is no reason to combine the prior art elements as claimed and that the invention produces unexpected results that rebuts the prima facie case. (Appeal Br. 11–15; Reply Br. 9–14.) We disagree for the reasons already discussed. Appellant also argues that “the

presently claimed compositions are simply not disclosed in [Friede]. Rather, . . . , [Friede] discloses long lists of alternative options from which one could select various elements. Thus, [Appellant's] surprising results are not merely inherent in an old composition that was known and used in the art.” (Reply 9.) To the extent this argument relates to the alleged unexpected results, we have already explained why that argument is unconvincing. To the extent Appellant's argument is that the cited references cannot inherently disclose the functional limitation relating to a “Th1” adjuvant because picking and choosing is required to arrive at the claimed invention, we are likewise unconvinced. Friede discloses a preferred form of its invention that is “potent in the induction of immune responses conventionally associated with the Th1-type immune system.” (FF3.) Furthermore, our reviewing court has held that inherency may supply a missing claim limitation in an obviousness as well as an anticipation analysis, so long as “the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 113 F.3d 1186, 1194–95 (Fed. Cir. 2014).

Accordingly, we affirm the Examiner's rejection of claim 5 as obvious over Friede, Hoffman, Van Scharrenburg, and Smith, as evidenced by the Tween 80 Product Information Sheet. Because our analysis differs from that of the Examiner's, however, we designate the affirmance as a new ground of rejection. Claims 6, 7, 11–15, 17–28, and 32, which were not separately argued, fall with claim 5.

SUMMARY

We reverse the Examiner's decision rejecting claims 1, 8–11, 16–18, 22, 23, 29, and 32 under 35 U.S.C. § 102(b) as anticipated by Friede.

We affirm the Examiner's decision rejecting claims 5–7, 11–15, 17–28, and 32 under 35 U.S.C. § 103(a) as unpatentable over Friede, Hoffman, Van Scharrenburg, and Smith, as evidenced by Tween 80 Product Information Sheet, and designate the affirmance a new ground of rejection.

We enter a new ground of rejection of claims 1 and 29 under 35 U.S.C. § 103(a) as obvious over Friede. We have not entered new rejections of the dependent claims, but in the event of further prosecution (see below), the Examiner should consider whether any of the dependent claims should also be rejected over the prior art.

TIME PERIOD FOR RESPONSE

This decision contains new grounds of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides “[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.”

37 C.F.R. § 41.50(b) also provides that Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new grounds of rejection to avoid termination of the appeal as to the rejected claims:

- (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new [e]vidence relating to the claims so rejected, or both, and have the matter reconsidered by the [E]xaminer, in which event the prosecution will be remanded to the [E]xaminer. . . .
- (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART; 37 C.F.R. § 41.50(B)