United States District Court,
N.D. Ohio, Eastern Division.

GLAXO WELLCOME, INC,
et al. Plaintiffs.
v.
BEN VENUE LABORATORIES, INC,
Defendant.

July 31, 1998.

Steven S. Kaufman, Kaufman & Cumberland, Cleveland, OH, Janet B. Linn, Stephen B. Judlowe, Brian P. Murphy, Robert G. Gibbons, Neil S. Goldstein, Albert Chin, Jason Aaron Lief, Regina Marie Ambery, Hopgood, Calimafde, Kalil & Judlowe, New York, NY, David B. Webster, Webster & Webster, Cleveland, OH, for Glaxowellcome Inc., plaintiff.

Steven S. Kaufman, Janet B. Linn, Stephen B. Judlowe, Brian P. Murphy, Robert G. Gibbons, Neil S. Goldstein, Albert Chin, Jason Aaron Lief, Regina Marie Ambery, David B. Webster, (See above), for Glaxo Group Limited aka Glaxo Limited Group, plaintiff.

Richard M. Knoth, Jayne L. Jakubaitis, Arter & Hadden, Cleveland, OH, David N. DeRoberts, Climaco, Climaco, Seminatore, Lefkowitz & Garofoli, Cleveland, OH, Richard L. Chinn, Richard D. Kelly, Jean-Paul Lavalleye, Frank J. West, Oblon, Spivak, McClelland, Maier & Neustadt, Arlington, VA, for Ben Venue Laboratories, Inc., defendant.

John P. Murtaugh, Pearne, Gordon, McCoy & Granger, Cleveland, OH, for John P Murtaugh, neutral.

OPINION AND ORDER

GWIN**, J.**

On March 17, 1998, this cause came on for trial before the Court, the parties having waived their right to a jury trial. After observing the demeanor of witnesses and hearing the evidence, the Court makes the following findings of fact and conclusions of law.

Plaintiffs Glaxo Wellcome, Inc. and Glaxo Group Limited bring this action and allege that Defendant Ben Venue Laboratories, Inc. infringed a patent owned by Glaxo. With that patent, Glaxo disclosed a higher pH level for a ranitidine injection used to treat stomach ulcers.

Defendant Ben Venue counterclaims and asks this Court to declare Glaxo's patent invalid. In claiming that Plaintiff Glaxo Wellcome's patent is invalid, Defendant Ben Venue says the claims were obvious and anticipated. Asserting Glaxo's claims were obvious and anticipated, Ben Venue says Glaxo's patent is invalid under 35 U.S.C. s. 103.

I. Factual background

Plaintiff Glaxo Wellcome claims Defendant Ben Venue infringed United States Patent No. 4,585,790 entitled "Pharmaceutical Compositions" (the '790 patent). Glaxo Wellcome obtained the '790 patent in 1986. In defense to Glaxo's patent infringement claim, Defendant Ben Venue says the '790 patent was obvious and anticipated by the prior art. If the '790 patent is anticipated or obvious, Defendant Ben Venue says the '790 patent is invalid and cannot support this infringement action.

Plaintiff Glaxo Wellcome is a major pharmaceutical company. Glaxo is the inventor and marketer of the anti-ulcer drug Zantac. Glaxo achieved much of its growth and success from this proprietary drug. Zantac is administered a number of different ways. The '790 patent involves an injectable application of Zantac.

Defendant Ben Venue Laboratories, Inc. is a subsidiary of Boehringer Ingleheim, a major international pharmaceutical firm. Boehringer Ingleheim is a research-based entity engaged in the research and development of innovative pharmaceutical products as well as the introduction of generic drugs.

As described, Plaintiff Glaxo Wellcome says Defendant Ben Venue infringes its patent rights under the '790 patent. Under the '790 patent, Glaxo Wellcome received rights to an injectable form of ranitidine with a higher pH level. FN1 Ranitidine is the principal agent of Zantac.

Ben Venue and its unincorporated division, Bedford Laboratories, each have filed an Abbreviated New Drug Application with the Food and Drug Administration ("FDA") for ranitidine injection. Defendant Ben Venue's abbreviated new drug applications 74-764 and 74-777 both seek FDA approval. Ben Venue seeks approval and intends to market this ranitidine injection before the expiration of the '790 patent.

In seeking to market this ranitidine injection, Ben Venue says Glaxo Wellcome's patent is invalid. Near December 28, 1995, Ben Venue told Glaxo of its intent to seek approval to market its ranitidine injection and argued that Plaintiff Glaxo Wellcome's patent was invalid for anticipation and obviousness. This lawsuit resulted.

A. Development of the '658 patent

Here, Plaintiff Glaxo Wellcome seeks protection for an injectable form of ulcer medication it developed. Ulcers involve a breakdown of the stomach's tissue and the exposure of that tissue to the very acidic stomach environment. Ulcers can cause great pain and can lead to severe complications.

In the early 1970s scientists discovered that drugs that reduced the hormone histamine (or "H^2 antagonist") were effective for treating ulcers. Glaxo developed ranitidine, an H^2 antagonist, for the treatment of ulcers. Glaxo developed ranitidine under the tradename Zantac. By use of the H^2 antagonist, ranitidine, Zantac lowers stomach acid and helps ulcers to heal.

Glaxo developed various methods for administering Zantac. After describing the oral formulation of Zantac, Glaxo developed an intravenous injection for the administration of Zantac. This intravenous injection can be used in emergency rooms where patients are not conscious. This intravenous injection can be used when patients are incapable of swallowing.

After developing an intravenous form of Zantac, Glaxo representatives applied for, and received, United States Patent 4,128,658 (the '658 Patent). The '658 patent disclosed a formulation of ranitidine for use in injections. The '658 patent expired December 5, 1995.

Over time, ranitidine deteriorates until it can no longer be used. With this deterioration, unused Zantac needs to be discarded. In developing an injection form of Zantac, Glaxo sought a formula that minimized the chemical breakdown of ranitidine. In seeking a formulation that minimized this chemical breakdown, Glaxo was aware that chemical stability (or shelf life) of a liquid or aqueous drug can be affected by temperature, solution pH, ionic strength of the solution, dielectric constant, the presence of oxygen, and the presence of light.

Thus in formulating Zantac, Glaxo sought to slow deterioration. By slowing the deterioration of ranitidine, Glaxo increased the chemical stability and prolonged the drug's shelf life. The ultimate goal was to maximize chemical stability and minimize the waste associated with a short shelf-life.

In applying for the '658 patent, Glaxo described an injectable form of ranitidine. The '658 patent described an aqueous injection solution for intravenous administration of ranitidine and water wherein the pH is adjusted to near 5.0.

In submitting the '658 patent, Glaxo said that the ranitidine injection was most stable at a pH level between 5 and 6, which Glaxo termed its "natural pH. " The '658 patent says the pH level is adjusted with dilute hydrochloric acid. Then, the '658 patent says the injection solution should be sterilized by autoclaving at 121 (deg.)C for 30 minutes.

Because the difference between the '658 patent and the '790 patent is the pH range, the Court need examine whether the '658 patent or other materials anticipated or made obvious the change in the pH level found in the '790 patent. In claiming that the pH level of the '790 patent was anticipated or obvious, Defendant Ben Venue makes several arguments. First, Defendant Ben Venue says the pH level of a formulation is generally known to have potential effect upon chemical stability. Second, Ben Venue says a publication issued before the the '790 patent, the Padfield Publication, specifically indicated that the stability of the '658 patent was affected by its pH level. Knowing that the pH level affected the stability of the '658 patent, Defendant Ben Venue says one skilled in the art would do a pH profile. After doing such a pH profile, Ben Venue argues that one skilled in the art would find that ranitidine in injectable formulation was most stable at a 6.5-7.5 pH level. Third, Defendant Ben Venue shows that the earlier '658 patent required autoclaving for sterilization. Because autoclaving causes the pH level of the '658 formulation to rise near the pH level of the '790 patent, Defendant Ben Venue says the pH level of the '790 patent is obvious or anticipated. FN2

B. The '790 patent

After describing ranitidine as most stable at pH levels betwen 5 and 6, Dr. John Padfield and Dr. Ian Winterborn undertook a further investigation of the stability of solutions of ranitidine hydrochloride. After this study, Drs. Padfield and Winterborn authored an article (the Padfield Publication) announcing that the chemical stability of the Zantac injection solution was most stable at its "natural pH."

As noted, Glaxo first stated that Zantac was most stable at its "natural pH level" of 5 or 6. However, further studies showed that chemical stability could be significantly improved by adjusting the pH level of ranitidine solutions to a pH level of approximately 7.

On May 11, 1984, Glaxo filed the '790 patent application in the name of inventors John M. Padfield and Ian K. Winterborn. In this patent application, Glaxo disclosed two prior art references: the '658 patent FN3 and the Padfield Publication. With studies showing ranitidine solution was most stable at a pH level near 7, Glaxo applied to the United States Patent and Trademark Office for approval of a patent for ranitidine at a pH level near 7.

The United States Patent and Trademark Office initially rejected the claims associated with the changed pH level as obvious and anticipated to one of ordinary skill in the art.FN4 As described, in deciding that the claims were obvious and anticipated, the Patent and Trademark Office had only the the '658 patent and the Padfield Publication as the prior art.

In response to the Patent and Trademark Office's rejection as obvious and anticipated, Glaxo filed an amendment to Claim 1. With its amendment, Glaxo argued that the pH level change was not obvious and anticipated. With its amendment, Glaxo said:

While there is no doubt that one of ordinary skill in the art would be able to adjust the pH of an aqueous based ranitidine formulation to a pH within the range claimed in the present application, there is nothing to suggest any reason or motivation for one of ordinary skill in the art to do this.

Despite Glaxo's argument that the prior art suggested a formulation with a pH level around 5.5 and the argument that there would be no reason for one skilled in the art to test stability at different pH levels despite the ease of such tests, the Patent and Trademark Office issued a final rejection of the patent claims.

After the final rejection of the patent claims, Glaxo requested reconsideration. At the reconsideration, Glaxo's attorney met with the primary Patent and Trademark Office examiner. Glaxo also submitted the declaration of Dr. John Padfield, one of the inventors. In his declaration, Padfield stated that increase of the pH level from 5.5 to 7.0 substantially increased stability.

After receiving the Padfield declaration, the Patent and Trademark Office allowed claims 13 and 14 but continued to disallow claims 1-11. In continuing to reject the broad majority of the claims, the examiner found the claims obvious and anticipated. The examiner concluded: "it is within the skill of the art to adjust the pH to the [claimed] range."

Glaxo disagreed and again sought allowance, filing a response on October 7, 1985. In that response, Glaxo argued that "[t]he test of obviousness is not 'obvious to try' various pH ranges, but the obviousness of the invention in its entirety."

On December 6, 1985, after reviewing Glaxo's response, the Patent and Trademark Office Examiner Friedman issued a finding that claims 1-11 and 13-14 were patentable.

II. Discussion of infringement issue

A. Claim construction

In the '790 patent issued to Dr. John M. Padfield and Dr. Ian K. Winterborn, Glaxo discloses and claims an improved pharmaceutical composition for aqueous ranitidine. In this disclosure, Glaxo raises the pH level from the 5.5 range disclosed in the '658 patent to the range of 6.5 to 7.5.

Plaintiff Glaxo Wellcome says that Defendant Ben Venue infringes the '790 patent. To decide if Ben Venue infringes the '790 patent, the Court must first construe the claim. After construing the claim, the Court must compare the claim to the product accused of infringement. Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 384 (1996).

The construction of a patent, including terms of art within its claim, is a question of law. See Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996). To resolve infringement, a court determines the scope and meaning of the claims and then decides if the party infringes those claims. To prove infringement, the plaintiff must show that the accused device includes every limitation of the claim or an equivalent of each limitation not literally met.

The language of the claims (plus equivalents of the claimed invention) defines the bounds of the patentee's exclusive rights. See Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 619-20 (Fed.Cir.1995) ("First, and most importantly, the language of the claim defines the scope of the protected invention"); Yale Lock Mfg. Co. v. Greenleaf, 117 U.S. 554, 559 (1886) ("The scope of letters-patent must be limited to the invention covered by the claim, and while the claim may be illustrated it cannot be enlarged by language used in other parts of the specification").

As to Abbreviated New Drug Application 74-764, Defendant Ben Venue does not contest infringement of claims 1-3, 6, 7, 11 and 12. Defendant Ben Venue does not contest that Glaxo has sustained its burden of proving an infringement of claims 1-3, 6-7, 11 and 12.FN5

With regard to Abbreviated New Drug Application 74-777, Defendant Ben Venue does not contest infringement of claims 1-7, 11 and 12 of the '790 patent, and acknowledges that Glaxo proves infringement of claims 1-7, 11 and 12 if the the '790 patent is valid.

As to infringement, the Court need decide if Abbreviated New Drug Application 74-764 infringes claim 4 of the '790 patent. In deciding whether Defendant Ben Venue infringes claim 4, the Court construes that claim to disclose:

"a pharmaceutical composition which is an aqueous formulation, containing an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof for treatment of conditions mediated through histamine H2-receptors, said formulation having a pH within the range of 6.5-7.5 and adjusted by means of suitable buffer salts."

As described, Claim 4 of the '790 patent discloses a composition having a pH of 6.5 to 7.5 which is adjusted by means of suitable buffer salts.

B. Literal infringement or infringement by equivalents

With Abbreviated New Drug Application 74-764, Ben Venue's solution contains sodium acetate trihydrate (sodium acetate), hydrochloric acid, sodium hydroxide, water and ranitidine. Defendant Ben Venue says that this sodium acetate, hydrochloric acid, and sodium hydroxide are not suitable buffer salts as claimed in Claim 4.

In suggesting that Abbreviated New Drug Application 74-764 does not have suitable buffer salts infringing

claims 4 or 5 of the '790 patent, Ben Venue shows that sodium acetate would not be used by one skilled in the art as a buffer for adjusting a pH within the range of 6.5 to 7.5. Acetic acid has a maximum efficacy (called pKa) of 4.7. Because acetic acid has a pKa of 4.7, it is not at its maximum buffering capacity within the pH range of 6.5 to 7.5. If used as a buffer within the pH range of 6.5 to 7.5, acetic acid would require higher concentrations of acetic acid to obtain buffering capacity. This use of higher salt concentrations is taught against by the desire to minimize unnecessary components in the formulation.

One skilled in the art would not choose to use sodium acetate trihydrate to buffer in the pH range of from 6.5 to 7.5. To use acetic acid in the pH range of 6.5 to 7.5 requires much higher amounts. Because the use of such higher amounts has accompanying deleterious effects, it is taught against. Those skilled in the art seeking to buffer a solution at a pH between 6.5 and 7.5 would consider a suitable buffer to be one which had maximum efficacy (called pKa) within the 6.5-7.5 range. Ben Venue's sodium acetate, HCl and sodium hydroxide system acts as an effective buffer at a pH significantly below 6.5, at 4.7. Accordingly, the composition containing sodium acetate, hydrochloric acid, and sodium hydroxide used by Ben Venue in Abbreviated New Drug Application 74-764 does not literally infringe claim 4 of the '790 patent.

Under the doctrine of equivalents, a patentee may proceed against the producer of a device "if it performs substantially the same function in substantially the same way to obtain the same result." Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 608 (1950) (*quoting* Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 42 (1929)). In reviewing infringement under the doctrine of equivalents, the Court should focus on the claim language. Vehicular Technologies Corp. v. Titan Wheel Intern., Inc., 141 F .3d 1084, 1088 (Fed.Cir.1998).

The Court finds that Defendant Ben Venue's Abbreviated New Drug Application 74-764 has substantial differences between the elements claimed and the accused product. The Court finds that claim 4 of the '790 patent is not infringed by the acetate buffer formulation under the doctrine of equivalents. Because one skilled in the art would not use acetic acid to buffer a pH within the range of 6.5 to 7.5, it is not equivalent.

III. Invalidity

A. Standard of review

The Court hereafter discusses whether the '790 patent is invalid as anticipated or obvious. If valid, the Court finds that Application 74-764 infringes claims 1-3, 6, 7, 11 and 12 of the '790 patent. If valid, the Court finds that Application 74-777 infringes claims 1-7, 11 and 12 of the '790 patent.

Defendant Ben Venue says the '790 patent is invalid as obvious or anticipated. A patent is presumed valid. Therefore, a party claiming that a patent is invalid has the burden of showing such invalidity. Invalidity must be proven by clear and convincing evidence. 35 U.S.C. s. 282. As described in Roper Corp. v. Litton Systems, Inc., 757 F.2d 1266 (Fed.Cir.1985):

The patent statute, 35 U.S.C. s. 282, is unambiguous: "A patent shall be presumed valid ... [T]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." A patent is born valid. It remains valid until a challenger proves it was stillborn or had birth defects, or it is no longer viable as an enforceable right.

Id. at 1270.

The presumption of validity is based on the presumption of administrative correctness of actions of the agency charged with examination of patentability. Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc., 98 F.3d 1563, 1569 (Fed.Cir.1996), *cert. denied,* 117 S.Ct. 1822 (1997); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1139 (Fed.Cir.1985) (the government agency is presumed to have done its job).

In addition to the general presumption of validity, when a party relies on art the examiner considered, that party bears the burden of overcoming the deference due a qualified government agency official presumed to have performed his or her job. American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed.Cir.), *cert. denied,* 469 U.S. 821 (1984).

The presumption of validity mandated by 35 U.S.C. s. 282 is applicable to all of the many grounds for challenging a patent's validity. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1570 (Fed.Cir.), *cert. denied,* 481 U.S. 1052 (1987).

B. Invalidity as anticipated by prior art

Defendant Ben Venue says the '790 patent is invalid as anticipated in the prior art. The doctrine of inherency asserts that a product or process lacks novelty if its claimed elements are embodied in prior art. If the prior art details the entire procedure or process it is said to anticipate the claimed product or process. 35 U.S.C. s. 102(a).

35 U.S.C. s. 102(a) reads in pertinent part:

"A person shall be entitled to a patent unless-

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent ..."

A patent claim is "anticipated" and, therefore, invalid when a single prior art reference discloses each and every limitation of claim. Disclosure need not be express, but may anticipate by inherency where it would be appreciated by one of ordinary skill in the art. Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043 (Fed.Cir.), *cert. denied,* 516 U.S. 988 (1995).

Defendant Ben Venue must prove anticipation by clear and convincing evidence. Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc., 34 F.3d 1048, 1052 (Fed.Cir.1994). A claim is anticipated and, therefore, invalid only when a single prior art reference discloses each and every limitation of the claim. Glaxo, 52 F.3d at 1047 (*citing* Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1571 (Fed.Cir.1986), *cert. denied sub nom.* Stora Kopparbergs Bergslags AB v. Crucible, Inc., 479 U.S. 1034 (1987)); Electro Med. Sys., 34 F.3d at 1052 (anticipation under s. 102 "requires the presence in a single prior art disclosure of each and every element of a claimed invention"); Shearing v. Iolab Corp., 975 F.2d 1541, 1544 (Fed.Cir.1992) (prior art reference must "disclose in advance of [the patentee's] invention each and every element of the ... patent's claims") (*citing* Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed.Cir.1991)).

As described, under 35 U.S.C. s. 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference. Akzo N.V. v. U.S. Intern. Trade Comm'n, 808 F.2d 1471,

1478 (Fed.Cir.1986), *cert. denied,* 482 U.S. 909 (1987); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1554 (Fed.Cir.1983), *cert. denied,* 469 U.S. 851 (1984). In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. In re Brown, 329 F.2d 1006, 1011 (C.C.P.A.1964). To anticipate, the prior art must place one of ordinary skill in possession of the claimed invention. In re Spada, 911 F.2d 705, 708 (Fed.Cir.1990); Seymour v. Osborne, 78 U.S. 516, 555 (1870) ("[T]he knowledge supposed to be derived from the publication must be sufficient to enable those skilled in the art or science to understand the nature and operation of the invention").

As to anticipation, Defendant Ben Venue says that the '658 patent and the Padfield Publication sufficiently disclose the pH level to allow one skilled in the art to use the 6.5 to 7.5 pH level. This argument fails.

First, the defense of anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference. Here, the '658 patent and the Padfield Publication only suggest that the stability of Zantac is affected by its pH level. Second, the prior art disclosure is not sufficient to place one of ordinary skill in possession of the claimed invention.

As described, Defendant Ben Venue seeks to invalidate the '790 patent on the basis that these claims are anticipated by the prior art (the Padfield Publication and the '658 patent).FN6 But this prior art does not expressly describe each and every element of the claims at issue. The '658 patent describes a natural pH level of 5.0 for the aqueous ranitidine solution. The '658 patent indicates this solution should be autoclaved. While autoclaving causes the pH level to rise, it does not expressly describe the pH level of the '790 patent.

Similarly, the Padfield Publication teaches that the pH level affects stability. But having indicated that the pH level affects stability, the Padfield Publication does not disclose each and every element of the claimed invention.

Because this prior art does not expressly describe all elements of the claims, Ben Venue must show that the prior art would cause one of ordinary skill in the art to appreciate it. Glaxo, 52 F.3d at 1047.

In Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264 (Fed.Cir.1991), the court described the rule controlling this:

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. In re Oelrich, 666 F.2d 578, 581 (C.C.P.A.1981) (*quoting* Hansgirg v. Kemmer, 102 F.2d 212, 214 (C.C.P.A.1939)) provides:

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Id. at 1268-69.

As to this showing, Ben Venue gives credible evidence that the greatest stability of injectable ranitidine is

inheriently at a 6.5-7.5 pH level. More difficult, Ben Venue must show that one skilled in the art would recognize this inherent level.

An anticipating reference must bear within its four corners "adequate directions for the practice" of the invention. If it "offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation." Dewey & Almy Chemical Co. v. Mimex Co., 124 F.2d 986, 989-990 (2d Cir.1942).

While Defendant Ben Venue shows evidence that injectable ranitidine would be inherently most stable at pH levels of 6.5-7.5, it fails to show that this would be recognized, understood and appreciated by one of ordinary skill in the art on the date that the invention was made. Continental Can Co., 948 F.2d at 1268-69 ("To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill").

The Zantac injection disclosed in the Padfield Article, and the ranitidine injection disclosed in Example 33b of the '658 patent do not inherently anticipate the '790 patent. The Padfield Article expressly discloses a ranitidine injection formulation at a "natural" pH of about 5.5. Example 33b discloses an injection made from ranitidine base and hydrochloric acid adjusted to a pH of 5.0. One of ordinary skill in the art would not have any reason to think that the stability of the formulations described in these publications could be improved at a pH of 6.5-7.5 and still contain an effective amount of ranitidine for treatment of ulcers.

Ben Venue's evidence does not show that the Padfield Publication and Example 33b of the '658 patent would be recognized as pointing to a pH level of 6.5-7.5. First, the Padfield Publication does not disclose or suggest the pH range of 6.5-7.5 in the '790 patent. Second, while Ben Venue gives evidence that those skilled in the art might have done pH profile tests, it fails to show by clear and convincing evidence that such tests would have been so recognized as necessary to persons of ordinary skill.

For these reasons, the Court finds that Defendant Ben Venue fails to show that the '790 patent is invalid as anticipated.

C. Invalidity as obvious

An invention must meet certain criteria in order to be eligible for a patent. For an invention to be patentable, it must be (1) of patentable subject matter, (2) useful, (3) new, and (4) nonobvious. 35 U.S.C. s.s. 101 -103. FN7

In Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), the Court described factors to be considered in making the obviousness determination:

Under s. 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be

patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18. *See also* Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62 (1969).

A new invention is not patentable unless it was nonobvious when it was made.

A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. s. 103.

In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety. *See* W.L. Gore & Assocs., 721 F.2d at 1551; *see also* Medtronic, Inc. v. Cardiac Pacemakers, Inc., 721 F.2d 1563, 1567 (Fed.Cir.1983).

Throughout the obviousness determination, a patent retains its statutory presumption of validity,FN8 and the movant retains the burden to show the invalidity of the claims by clear and convincing evidence as to underlying facts. *See* Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc., 45 F.3d 1550, 1555 (Fed.Cir.1995).

For a finding of obviousness, the prior art need not appear in a single reference. But if various pieces of prior art are relied upon, the idea of combining elements must flow logically. Shanklin Corp. v. Springfield Photo Mount Co., 521 F.2d 609, 616 (1st Cir.1975)(The defense of obviousness is less strict than that of anticipation, which requires substantial identity of all elements between a single prior art reference and the claimed invention. Prior art that is insufficiently similar to support anticipation may still render the claimed patent obvious in combining various elements), *cert. denied,* 424 U.S. 914 (1976).

For prior art to make an invention obvious, the prior art must be enabling. *See* Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1471 (Fed.Cir.1997)("In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method").

Because neither the '658 patent nor the Padfield Publication explicitly describe the 6.5-7.5 pH level, Ben Venue had the burden to prove these references would suggest to one of ordinary skill in the art the need to do the pH profile. In re Dow Chem. Co., 837 F.2d 469, 473 (Fed.Cir.1988); *cf*. Miles Lab., Inc. v. Shandon, Inc., 997 F.2d 870, 878 (Fed.Cir.1993) ("The differences between the prior art and [the patent claim] were minor and achievable by simple modification. Moreover, the prior art references collectively suggest the engineering necessary to achieve these modifications"), *cert. denied,* 510 U.S. 1100 (1994).

Defendant Ben Venue thus suggests an "obvious to experiment" standard for obviousness. In considering Ben Venue's argument that it would be obvious to experiment, the Court must not use hindsight. To avoid an improper use of hindsight, there must be a reason or suggestion in the art for the experiment. Interconnect Planning Corporation v. Feil, 774 F.2d 1132, 1143 (Fed.Cir.1985).

The defendant argues that it would have been obvious to one of ordinary skill in the art to perform a pH profile to determine the pH range over which the solution was most stable. This would have led one of ordinary skill in the art to the claimed pH range.

Defendant Ben Venue's argument has force. Ben Venue gave testimony from Dr. Stanley Hem. In his testimony, Dr. Hem testified credibly that one skilled in the art would perform a pH profile to determine the pH range over which the solution was most stable. In giving the opinion that such a test would be done, Dr. Hem cited the ease of such a test and statements from the Padfield Publication that the pH level affected stability.

Despite Defendant Ben Venue's strong evidence, the Court does not find that Ben Venue shows the '790 patent invalid by *clear and convincing* evidence. Without the prescience of hindsight, the Padfield Publication suggestion that pH matters does not sufficiently suggest the '790 patent pH level.

For these reasons, the Court finds that Defendant Ben Venue fails to show that the '790 patent is invalid as obvious.

IV. Conclusion

For the foregoing reasons, the Court finds that Application 74-764 infringes claims 1-3, 6, 7, 11 and 12 of the '790 patent. The Court finds that Application 74-764 does not infringe claim 4 of the '790 patent. The Court finds that Application 74-777 infringes claims 1-7, 11 and 12 of the '790 patent.

For the foregoing reasons, the Court finds that Defendant Ben Venue does not show the '790 patent to be invalid by clear and convincing evidence.

IT IS SO ORDERED.

FN1. The pH level of an aqueous solution is a measure of its hydrogen ion content and, therefore, its relative acidity or alkalinity, a pH of 7 being neutral.

FN2. Autoclaving will cause a solution of ranitidine with a pH of 5.0 to rise to a pH of 6.2-6.5.

FN3. Specifically, Glaxo disclosed Example 33b and 33d of the '658 patent.

FN4. The Court finds that a person of ordinary skill in the area of technology involved in this case would be a formulation scientist possessing a bachelor of science degree in either pharmacy, chemistry or biology. A minimal amount of experience or an advanced degree, such as a master's or doctorate, also would be required.

FN5. Claim 1 of the '790 patent is an independent claim. It claims "a pharmaceutical composition which is an aqueous formulation, containing an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof for treatment of conditions mediated through histamine H2-receptors, said formulation having a pH within the range of 6.5-7.5.

Claims 2-5 are dependent on claim 1. Claim 2 is "a pharmaceutical composition according to claim 1 having

a pH in the range 6.7 to 7.3." Claim 3 is "a pharmaceutical composition according to claim 1 having a pH in the range 6.8 to 7.1."

Claim 4 adds a requirement to the last element of claim 1, requiring that "said pH is adjusted by means of suitable buffer salts."

Claim 5 narrows claim 4 by specifying the use of particular buffer salts to adjust pH. These buffer salts are potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

FN6. Defendant Ben Venue specifically cites Example 33b of the '658 patent.

FN7. 35 U.S.C. s. 103 provides, in part:
(a) 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.

FN8. *See* 35 U.S.C. s. 282.

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