

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte THOMAS P. ZIMMERMAN, VALERY NOVOKHATNY,
SHAN JIANG and JAMES COLANDENE

Appeal 2007-0545
Application 10/143,112
Technology Center 1600

Decided: February 19, 2008

Before DONALD E. ADAMS, LORA M. GREEN,
and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-43.¹ We have jurisdiction under 35 U.S.C. § 6(b). Claim 1 is representative of the claims on appeal, and reads as follows:

¹ A hearing for this Appeal was held on January 22, 2008.

1. A fibrinolytic composition comprising:
a reversibly inactivated, acidified plasmin, the plasmin being substantially free of a plasminogen activator;
a low buffering capacity buffer; and
optionally, a stabilizing agent,
wherein the composition is a solution suitable for pharmaceutical use that can be raised to physiological pH by adding no more than 5 volumes of serum to the solution relative to a volume of the solution.

The Examiner relies upon the following references:

Diedrichsen	US 4,462,980	Jul. 31, 1984
Wu	US 4,774,087	Sep. 27, 1988
Reich	US 5, 407,673	Apr. 18, 1995
Hirsh	US 5,767,269	Jun. 16, 1998
Yago	US 5,879,923	Mar. 9, 1999

Robbins, "Purification of Human Plasminogen and Plasmin by Gel Filtration on Sephadex and Chromatography on Diethylaminoethyl-Sephadex," *The Journal of Biological Chemistry*, Vol. 238, No. 3, pp. 952-962 (1963).

http://www.lakesidepress.com/pulmonary/books/physiology/chap7_1.htm, Chapter 7: Acid-Base Balance.

We affirm.

DISCUSSION

Claim Interpretation

Our mandate is to give claims their broadest reasonable interpretation. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). "An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." *In re Zletz*, 893 F.2d 319, 322 (Fed. Cir. 1989).

Claim 1 requires: 1) a reversibly inactivated, acidified plasmin, the plasmin being substantially free of a plasminogen activator; 2) a low buffering capacity buffer; and 3) optionally, a stabilizing agent, wherein the solution is suitable for pharmaceutical use and can be raised to physiological pH by adding no more than 5 volumes of serum to the solution relative to a volume of the solution.

As to the “reversibly inactivated, acidified plasmin,” the Specification teaches that limitation “refers to any catalytically active form of plasmin capable of proteolytically cleaving fibrin when under physiological conditions, but reversibly inactivated when placed at a pH between about 2.5 to about 4.0.” (Specification 12.) The Specification does not specifically define the amount of plasminogen activator that may be present and still meet the limitation that the plasmin be “substantially free of plasminogen activator.” The Specification teaches, however, that highly pure plasmin is >95% pure (*id.* at 19). Thus, we interpret “substantially free of plasminogen activator” as reading on fibrinolytic compositions that may contain up to about 5% plasminogen activator.

As to the low buffering capacity buffer, the Specification teaches “[b]uffers employed in the present invention include such low buffering capacity buffers which are present in the composition at a concentration which would allow the pH of the composition to be changed to a physiological pH by contacting body fluids.” (*Id.* at 8.) According to the Specification, the buffer may be a low buffering capacity acid such as hydrochloric acid (*id.*).

As to the stabilizing agent, the Specification teaches that the stabilizing agent may be a salt, such as sodium chloride (*id.*).

As to the requirement that the solution be “suitable for pharmaceutical use,” the Specification teaches that a “pharmaceutically acceptable carrier” is “any carrier that is physiologically tolerated by a recipient human or animal including, but not limited to, water, salt solutions, physiological saline, or any other liquid or gel in which a fibrinolytic agent such as plasmin may be dissolved or suspended.” (*Id.* at 10.)

Rejection under 35 U.S.C. § 102(b)

Claims 1, 3, 4, 6, 7, 9-13, 17-22, 24, 25, 27-31, 35-38 and 40-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated Robbins (Answer 3-8). As Appellants do not argue the claims separately, claims 3, 4, 6, 7, 9-13, 17-22, 24, 25, 27-31, 35-38 and 40-43 stand or fall with claim 1. 37 CFR § 41.37(c)(1)(vii). Thus, we focus our analysis on claim 1.

The Examiner relies on Robbins for teaching the composition of claim 1 (Answer 4). According to the Examiner, Robbins prepares the plasmin by activating the proenzyme with trace quantities of urokinase in glycerol, and the plasmin is then purified to “a high state of purity” on DEAE-Sephadex™ columns. (*Id.* at 4-5) Robbins is also relied upon for teaching that the plasminogen activator, urokinase, “cannot be detected by enzymatic methods in any of the plasmin preparations.” (*Id.* at 5 (quoting Robbins, p. 957, first column).) The Examiner refers to a composition taught by Robbins containing “purified plasmin (No. 47) in 0.001 N HCl containing 0.1M NaCl, pH 2.8, at 20°C,” which, the Examiner asserts, “appears to be one and the same fibrinolytic composition disclosed and instantly claimed by Appellant.” (Answer 5.) The Examiner also states that “the fibrinolytic composition taught by Robbins is a solution suitable for pharmaceutical use,

since there is nothing contained therein the Robbins' composition to preclude pharmaceutical use." (*Id.*)

The burden is on the Examiner to set forth a *prima facie* case of unpatentability. *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). “[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

We find that the composition disclosed by Robbins (p. 958, second column, first full paragraph) of plasmin (No. 47) in 0.001N HCl containing 0.1M NaCl, pH 2.8, at 20°C, meets all of the limitations of the composition of claim 1. As noted in the claim interpretation, the low buffering capacity buffer may be an acid such as hydrochloric acid (HCl), and the stabilizing agent may be a salt, such as sodium chloride (NaCl). The Examiner presents calculations showing that the solution may be raised to physiological pH by adding no more than 5 volumes of serum to the solution relative to a volume of the solution (Answer 6-8), and Appellants do not refute those calculations. In addition, as the plasmin was purified to high purity using DEAE-Sephadex™ columns, and as Robbins teaches that plasminogen activator could not be detected by enzymatic methods in any of the plasmin preparations, we find that the limitation of being “substantially free of plasminogen activator” has been met. Moreover, as the pH of the solution is 2.8, and as the Specification teaches that plasmin is reversibly inactivated at a pH of about 2.5 to 4.0, the solution of Robbins also meets the limitation of

“a reversibly activated, acidified plasmin.” Finally, we agree with the Examiner’s finding that there is nothing contained in the Robbins’ composition to preclude pharmaceutical use, as there is nothing in the solution that would not be physiologically tolerated by a recipient human or animal.

Appellants argue that “Robbins . . . fails as an anticipatory reference because it does not disclose any plasmin solution in ‘a low buffering capacity buffer.’” (Br. 4.) Appellants assert that “Robbins’ notations of what the samples include (e.g., 0.001 N HCl, 0.1 M NaCl) do not necessarily teach that standard or high buffering capacity buffers, e.g., Tris or phosphate buffers, are not present.” (Reply Br. 6.) According to Appellants, “[b]ased on the manner in which Robbins describes various plasmin and plasminogen compositions throughout the reference, it does not appear that Robbins necessarily discloses *every* component of these compositions, but, rather, Robbins may only selectively disclose those components and parameters that are relevant to the particular analysis or use intended for the solution or sample being discussed.” (*Id.* at 6-7.) Appellants specifically refer to Robbins discussion of dialysis of plasmin samples at a specific pH, while failing to refer to the other components of the dialysis buffer (*Id.* at 7, referencing Robbins, p. 956). Appellants therefore conclude “[i]n view of the lack of clarity as to whether Robbins discloses all of the components of any particular composition, including the particular analytical sample specified by the Examiner, it cannot be concluded that a low buffering capacity buffer would necessarily be present in any of the compositions disclosed by Robbins.” (Reply Br. 7.)

Appellants' arguments are not convincing. Robbins teaches a plasmin composition comprising purified plasmin in 0.001 N HCL containing 0.1M NaCl, pH 2.8, at 20°C (Robbins, p. 958, second column, first full paragraph). As discussed above, the hydrochloric acid (HCl) is a "low buffering capacity buffer" (Specification 8). In addition, we do not agree with Appellants that Robbins has not disclosed all of the components of the composition. One of ordinary skill, reading the disclosure of a plasmin composition comprising purified plasmin in 0.001 N HCL containing 0.1M NaCl, pH 2.8, at 20°C, would read that as disclosing all of the components of the solution.

The portions of Robbins which Appellants point to as not "appearing" to disclose all of the components are not related to the composition relied upon to anticipate the composition of claim 1. Moreover, the passages relied upon by Appellants as not disclosing all of the components of the compositions do not cast doubt on our finding of anticipation.

Finally, a review of the reference as a whole reveals that Robbins makes clear when all of the components of the solutions being used are recited. For example, Robbins teaches a buffer used to equilibrate Sephadex columns (p. 953, bottom of second column, ("0.00005 N HCl, pH 3.5, 4°C")), as well as the components of the plasmin solution being relied upon as anticipating claim 1 (p. 958, bottom of second column, ("plasmin (No. 47) in 0.001 N HCl containing 0.1 M NaCl, pH 2.8, at 20°C")).

Appellants also argue that the means of detecting urokinase (the plasminogen activator) "was not adequate to detect amounts of urokinase low enough to establish that any compositions therein were 'substantially free of plasminogen activator,'" as the accuracy of the method used to

measure urokinase is \pm 10% (Reply Br. 5). According to Appellants, their teaching “regarding the use of immobilized urokinase for plasminogen activation, and the further purification of plasmin using a benzamidine affinity step, would inform one of ordinary skill in the art as to the meaning of the phrase ‘substantially free of a plasminogen activator’ as recited in the pending claims.” (*Id.* at 5-6.)

First, as noted in the claim interpretation section, we interpret “substantially free of plasminogen activator” as reading on solutions that may contain up to about 5% plasminogen activator. Moreover, while the accuracy of the method used by Robbins to measure urokinase may be \pm 10%, Appellants have not provided any evidence or reasoning explaining why the ordinary artisan would not expect that a plasmin solution, in which the plasmin has been activated and purified according to Robbins, would contain more than about 5% plasminogen activator. As pointed out by the Examiner (Answer 4-5), Robbins prepares the plasmin by activating the proenzyme with trace quantities of urokinase in glycerol, and then purifying the plasmin to “a high state of purity” on DEAE-SephadexTM columns, such that the plasminogen activator, urokinase, cannot be detected by enzymatic methods in any of the plasmin preparations. Thus, as the Examiner has provided evidence and scientific reasoning that the composition of Robbins meets the limitations of the composition of claim 1, the burden shifts to Appellants to demonstrate that they are different. *Spada*, 911 F.2d at 708.

Finally, Appellants argue that Robbins does not teach a solution that is suitable for pharmaceutical use (Reply Br. 8). According to Appellants, the solution was prepared solely for analytical purposes, and “one of ordinary skill in the art would recognize that such solutions would not be ‘suitable for

pharmaceutical use.’’’ (*Id.*) Appellants assert that “[t]hroughout the [S]pecification, Appellants make clear that ‘suitable for pharmaceutical use’ means that the compositions must be suitable for intravenous administration.” (*Id.* at 9.) Appellants argue further that “it is well known in the art that preparation of a solution ‘suitable for pharmaceutical use,’ especially where such ‘pharmaceutical use’ is taught as including intravenous administration to humans, involves much more than is involved in preparing a solution for analytical purposes according to a protocol expressly relating to such processes.” (*Id.* at 10.)

Appellants’ arguments are not commensurate in scope with the invention claimed in claim 1, and thus are not persuasive. Consistent with the Specification, we have interpreted “suitable for pharmaceutical use” as being physiologically tolerated by a recipient human or animal. Appellants have not provided any evidence or argument why a solution comprising plasmin in 0.001 N HCL containing 0.1M NaCl, pH 2.8, at 20°C, would not be physiologically tolerated by a human or animal.

Rejection under 35 U.S.C. § 103(a)

Claims 1-43 stand rejected under 35 U.S.C. § 103(a) as being obvious over Robbins as combined with Wu, Reich, Hirsh, Yago, and Diedrichsen.

As Appellants did not argue the claims separately, claims 2-43 stand or fall with claim 1. As we have already found that claim 1 is anticipated by Robbins, and as anticipation is the epitome of obviousness, *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002), we also affirm this rejection.

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CONCLUSION

In summary, we affirm the rejection of claims 1, 3, 4, 6, 7, 9-13, 17-22, 24, 25, 27-31, 35-38 and 40-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated Robbins, and the rejection of claims 1-43 stand rejected under 35 U.S.C. § 103(a) as being obvious over Robbins as combined with Wu, Reich, Hirsh, Yago, and Diedrichsen.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a) (1)(iv)(2006).

AFFIRMED

Ssc:

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