

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JENNIFER L. SCHMITKE, DONGHAO CHEN,
RICHARD P. BATYCKY, and DAVID A. EDWARDS

Appeal 2007-0854¹
Application 10/179,463
Technology Center 1600

Decided: July 24, 2007

Before DONALD E. ADAMS, LORA M. GREEN, and NANCY J. LINCK,
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 5, 7-18, 26, 28-42, 51, 53-64, and

¹ Heard June 5, 2007.

66-74.² We have jurisdiction under 35 U.S.C. § 6(b). Claims 5 and 51 are representative of the claims on appeal, and read as follows:

5. A formulation having particles comprising, by weight, 75% DPPC, 15% insulin and 10% sodium citrate.

51. A method of delivering an effective amount of insulin to the pulmonary system, comprising:

- (a) providing a mass of particles comprising by weight, 75% DPPC, 15% insulin and 10% sodium citrate; and
- b) administering via simultaneous dispersion and inhalation the particles, from a receptacle having the mass of the particles, to a human subject's respiratory tract, wherein release of the insulin is rapid.

The Examiner relies upon the following art in rejecting the claims:

Edwards	US 5,985,309	Nov. 16, 1999
Patton	US 5,997,848	Dec. 7, 1999

We affirm.

ISSUE

The Examiner contends that the invention as claimed is obvious over the combination of Edwards and Patton, and that Appellants have not rebutted the prima facie case.

Appellants contend that the Declaration of Jennifer L. Schmitke submitted under 37 C.F.R. § 1.132 and dated April 20, 2004 rebuts the Examiner's prima facie case of obviousness by demonstrating that the claimed composition has unexpected properties.

² This case is related to USSN 09/888,126, Appeal No. 2007-0913. Both Appeals were heard together, and have been considered and decided concurrently.

Thus, the issue is does the evidence submitted by Appellants demonstrate unexpected results as to the insulin formulation being claimed and thus rebut the Examiner's case of prima facie obviousness.

FACTS

The Examiner rejected claims 5, 7-18, 26, 28-42, 51, 53-64, and 66-74 under 35 U.S.C. § 103(a) as being obvious over Patton in view of Edwards (Office Action mailed August 11, 2004, 2).³

The Examiner relies on Patton for teaching the systemic delivery of insulin to a mammalian host through the inhalation of a dry powder that is rapidly absorbed through the alveolar regions of the lung (Office Action dated August 11, 2004, 2). The dry powder containing insulin is prepared by dissolving insulin in an aqueous buffer to form a solution and then spray drying the solution to produce substantially amorphous particles (*id.*). According to the Examiner, the pharmaceutical carrier, which may be an amino acid such as glycine, lysine, etc., may be optionally dissolved in the buffer, typically a citrate buffer such as sodium citrate, to form a homogenous solution, "wherein spray drying of the solution produces individual particles comprising insulin, carrier buffer, and any other compounds which were preset in the solution." (*Id.* at 2-3.)

Patton is also cited for teaching that dry powders of insulin that may be used include amorphous insulin, crystalline insulin, and mixtures thereof

³ Claims 5, 7-18, 26, 28-42, 51, 53-64, and 66-74 also stood rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending 10/179,463 in view of Patton (Office Action mailed August 11, 2004, 5). The rejection was withdrawn in the Answer upon the filing of a terminal disclaimer (Answer 6).

(*id.* at 2). The insulin concentration may range from 5 to 95%, preferably from 20 to 80%, with the carrier material ranging from 5 to 95% (*id.* at 3). The Examiner notes that “Patton, while teaching amino acids as carriers, lacks disclosure on DPPC.” (*Id.*)

Edwards is cited for teaching particles “incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, methods of preparation, and administration.” (*Id.*). Surfactants include dipalmitoylphosphatidylcholine (DPPC), and exemplary hydrophilic or hydrophobic complexes include insulin and protamine (*id.*). Moreover, according to the Examiner, the formulations of Edwards may include one or more excipients such as sugars, proteins, and surfactants (*id.* at 4). In addition, “Edwards discloses that administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example greater than 5 micron in mean diameter. The particles can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device.” (*Id.*)

The Examiner cites Example 9 of Edwards, which discloses particles containing 60% DPPC, 2% insulin, 19% albumin, and 19% lactose (*id.*). The particles are made from solutions of the ingredients, which are combined and spray dried to produce the particles (*id.*).

The Examiner concludes:

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the formulations of Patton containing insulin, buffers and carriers with insulin formulations and method of delivering the

insulin formulations to the lung as taught by Edwards and to have implemented DPPC as the carrier, since it was disclosed that DPPC is an exemplary surfactant, naturally occurring in the lung.

Id. at 4-5.

In the Appeal Brief, Appellants do not contest the prima facie case of obviousness. Instead, Appellants argue that “the evidence of record establishes significant unexpected results. Simply, the evidence establishes that the specific amounts of these components are critical. Thus the selection of presently claimed approximate amounts of 75% DPPC, 15% insulin and 10% citrate combination is patentable over the myriad of possible combinations derived from the combination of Patton and Edwards.” (Br. 3).

Appellants refer to Table 1 of the 132 Declaration, stating that formulations with an Emitted Dose (ED) greater than 90% are stable at standard conditions, and that formulations 2, 3 and 7⁴ fall into that category (Br. 5). But when the temperature and humidity were raised to 30°C/80% relative humidity (RH), according to Appellants, only formulations 2 and 7 met the target of an excellent ED at standard conditions and good retention of ED at the higher temperature and humidity, while formulations 3, 5, and 6 did not (*id.*). Thus, Appellants assert, “[w]hat was discovered was that the 15% insulin formulation unexpectedly withstood extreme conditions as compared to the 10% insulin formulation.” (*Id.* at 6.) Appellants argue that “[t]he robustness of a formulation at different environmental conditions was

⁴ Formulation 7 is the formulation of the instantly claimed invention.

considered a critical factor in identifying the chemical compositions that are suitable from a patient safety perspective.” (*Id.* at 10.)

Appellants conclude that the “132 declaration clearly shows that the criticality of the presently claimed formulation (not a *range* of formulations as described by the Examiner, but instead a superior *single species* of formulation), having particles comprising, by weight, approximately 75% DPPC, approximately 15% insulin and approximately 10% sodium citrate possesses unexpected properties as compared to formulations that are even *closer* than those of the combination of prior art cited by the Examiner.” (*Id.* at 6 (emphasis in original).)

The 132 Declaration of Jennifer Schmitke states at page 2 that the goal of the study “was to evaluate the dose delivery (emitted dose and aerodynamic particle size distribution) of representative formulations having a DPPC/sodium citrate excipient base at selected temperature and humidity conditions.” Table 1 on page 4 of the Declaration summarizes the emitted dose results of the selected DPPC based powders at 23°C/30%RH and 30°C/80% RH.

Formulations 1 and 2 are both 60% DPPC, 10% sodium citrate, and 30% insulin; yet at 23°C/30% RH, Formulation 1 exhibited an ED of 78(3),⁵ while Formulation 2 showed an ED of 94(2). At 30°C/80% RH, Formulation 1 exhibited an ED of 53(10), while Formulation 2 exhibited an ED of 71(7). Similarly, Formulations 4 and 5 were both 87% DPPC, 10% sodium citrate, and 10% insulin, and at 23°C/30% RH, Formulation 4 exhibited an ED of 83(2), and Formulation 5 showed an ED of 87(3). At 30°C/80% RH, Formulation 4 exhibited an ED of 48(11), while Formulation

⁵ Standard deviations are shown in the parenthesis.

5 exhibited an ED of 61(6). Formulation 7, which is 75% DPPC, 10% sodium citrate, and 15% insulin, *i.e.*, the claimed formulation, exhibited an ED of 93(1) at 23°C/30% RH, and an ED of 69(9) at 30°C/80% RH.

The Specification teaches “[f]ormulations having particles comprising, by weight, approximately 40% to approximately 60% DPPC, approximately 30% to approximately 50% insulin and approximately 10% sodium citrate.” (Specification 3). Also disclosed are:

Formulations having particles comprising, by weight, approximately 75% to approximately 80% DPPC, approximately 10% to approximately 15% insulin and approximately 10% sodium citrate In one embodiment, the particles comprise, by weight, 75% to 80% DPPC, 10% to 15% insulin and 10% sodium citrate. In another embodiment, the particles comprise, by weight, 75% DPPC, 15% insulin and 10% sodium citrate. In yet another embodiment, the particles comprise, by weight, 80% DPPC, 10% insulin, and 10% sodium citrate.

(*Id.*)

In addition, in the human clinical trial described in the Specification, a dry powder formulation of 60% DPPC, 30% insulin, and 10% citrate was used (*id.* at 51-52). The Specification does not disclose the criticality of formulations of approximately 75% DPPC, approximately 15% insulin and approximately 10% sodium citrate.

PRINCIPLES OF LAW

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or

argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (citations omitted).

The burden of demonstrating unexpected results rests on the party asserting them, and “it is not enough to show that results are obtained which differ from those obtained in the prior art; that difference must be shown to be an *unexpected* difference.” *In re Klosak*, 455 F.2d 1077, 1080, 173 USPQ 14, 16 (CCPA 1972). Moreover, it has been long held that “even though applicant’s modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges ‘produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.” *In re Huang*, 100 F.3d 135, 139, 40 USPQ2d 1685, 1688 (Fed. Cir. 1996) (quoting *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (1955), and citing *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990)).

ANALYSIS

As to the prima facie case of obviousness, Appellants do not contest it in the Brief,⁶ thus, for the purposes of this Appeal, we conclude that Appellants concede that the Examiner has met the burden of establishing a prima facie case of obviousness.

⁶ Appellants state in the Reply Brief at page 2 that they have not admitted, either explicitly or inferentially, that the Examiner has established a prima facie case of obviousness. But as they do not point to any arguments made in the Appeal Brief attacking the prima facie case, and also do not present any argument as to why the Examiner failed to establish a prima facie case in the Reply Brief, we find that Appellants have conceded the merits of the prima facie case for purposes of this Appeal. 37 C.F.R. § 41.37(c)(1)(vii).

We find that Appellants have not demonstrated that the formulation of claim 5 has unexpected properties so as to rebut the prima facie case of obviousness, and the rejection is affirmed.

As set forth above, Table 1 of the 132 Declaration, Formulations 1 and 2 are identical (both 60% DPPC, 10% sodium citrate, and 30% insulin). Yet at 23°C/30% RH, Formulation 1 exhibited an ED of 78(3), while Formulation 2 showed an ED of 94(2), and at 30°C/80% RH, Formulation 1 exhibited an ED of 53(10), while Formulation 2 exhibited an ED of 71(7). These results demonstrate that for the *same* formulation, there was substantial variability between the tests. Given the above, Formulation 2 would meet the desired criteria of stability, yet formulation 1 would not, even though they are both 60% DPPC, 10% sodium citrate, and 30% insulin.

In the Declaration, the Declarant states at page 4 that Formulation 1 was not considered to be representative of the formulation, so consequently the testing was run again using clinical lot capsules, designated as Formulation 2. The Declarant does not explain, however, how formulations 1 and 2 differ, nor does the Declarant explain why such disparate results were obtained.

Formulation 5, which is 87% DPPC, 10% sodium citrate, and 10% insulin, at 23°C/30% RH exhibited an ED of 87(3), and at 30°C/80% RH, exhibited an ED of 61(6). Formulation 7, which is 75% DPPC, 10% sodium citrate, and 15% insulin, *i.e.*, the claimed formulation, exhibited an ED of 93(1) at 23°C/30% RH, and an ED of 69(9) at 30°C/80% RH. However, the ED values between Formulations 5 and 6 differ very little (if at all) when the standard deviation is taken into consideration. At 23°C/30% RH, Formulation 5 had an ED of 87(3), and an ED of 90 would be within an ED

of 87 with a standard deviation of 5. Similarly, Formulation 7 exhibited an ED of 93(1), which would also include an ED of 92. The difference between an ED of 90 and 92, we find, is more a difference in kind than a difference in degree, which is required to support a finding of unexpected results. Likewise, at 30°C/80% RH, Formulation 5 has an ED of 61(6), and Formulation 7 has an ED of 69(9). Thus, at 30°C/80% RH, the ED of Formulations 5 and 7 overlap when the standard deviation is taken into consideration.

Thus, given that the same formulation, *i.e.*, Formulations 1 and 2, gave very disparate results, and given that there is little difference between Formulation 5, which is 10% insulin, and Formulation 7, *i.e.*, the formulation of claim 5, we find that Appellants' 132 Declaration does not demonstrate that the formulation of claim 5 exhibits properties that are unexpected.

CONCLUSIONS OF LAW

We conclude that the Examiner has set forth a prima facie case of obviousness that has not been contested by Appellants, and that the Declaration of Jennifer L. Schmitke, submitted under 37 C.F.R. § 1.132, does not demonstrate unexpected results sufficient to rebut the prima facie case.

CLAIMS 51, 53-64, AND 66

Appellants argue that claim 51 is separately allowable, because "Claim 51 recites simultaneous inhalation and dispersion of the particles from a receptacle containing the particles (e.g., breath actuated

administration,” and that “[n]either Patton nor Edwards disclose or make obvious this feature.” (Br. 10.)

The Specification teaches at pages 30 and 31 that “[v]arious suitable devices and methods of inhalation which can be used to administer particles to a patient’s respiratory tract are known in the art,” and lists a number of suitable prior art inhalers, as well as “others, such as those known to those skilled in the art.” In addition, both Patton (for example, see the abstract) and Edwards (see, for example, column 25, Example 12) teach the delivery of particles of insulin to the lungs, but do not specifically teach the use of a breath-actuated inhaler.

The panel cites Bacon (U.S. Patent No. 5,503,144, issued April 2, 1996) to demonstrate that breath actuated dry powder inhalers and their use were known in the art, and thus, it would have been obvious to dispense the formulation of claim 51 using any dry powder inhaler known to the ordinary artisan, such as that taught by Bacon. The rapid release of insulin would be an inherent result of the delivery of the formulation of claim 5 to lungs using such breath-actuate, dry powder inhalers. Because our reasoning differs from that of the Examiner, and in order to give Appellants an opportunity to respond, we designate this affirmance as new grounds of rejection under 37 C.F.R. § 41.50(b).

CONCLUSION

In summary, we affirm the rejection of claims 5, 7-18, 26, 28-42, 51, 53-64, and 66-74. Because our reasoning as to claims 51, 53-64, and 66 differs from that of the Examiner, we designate the rejection as to those claims only as new grounds of rejection.

Regarding the affirmed rejection(s), 37 C.F.R. § 41.52(a)(1) provides "[A]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the Examiner's rejection(s) of one or more claims, this decision contains a new ground 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 the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground 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 evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the

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prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

AFFIRMED; 37 C.F.R. § 41.50(b)

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